



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>7</sup> :  <b>C07D 401/12, 401/06, 211/14, 211/22,  A61K 31/445, A61P 11/00, 19/00, 31/00</b></p>	<b>A1</b>	<p>(11) International Publication Number: <b>WO 00/58305</b></p> <p>(43) International Publication Date: 5 October 2000 (05.10.00)</p>		
<table border="0" style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>(21) International Application Number: PCT/SE00/00563</p> <p>(22) International Filing Date: 22 March 2000 (22.03.00)</p> <p>(30) Priority Data:  9901117-3                      26 March 1999 (26.03.99)                      SE  9902194-1                      10 June 1999 (10.06.99)                      SE</p> <p>(71) Applicant (for all designated States except MG US): AS-  TRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate,  London W1Y 6LN (GB).</p> <p>(71) Applicant (for MG only): ASTRAZENECA AB [SE/SE];  S-151 85 Södertälje (SE).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BAXTER, Andrew  [GB/GB]; AstraZeneca, R &amp; D Charnwood, Bakewell  Road, Loughborough, Leisc. LE11 5RH (GB). BROUGH,  Stephen [GB/GB]; AstraZeneca, R &amp; D Charnwood,  Bakewell Road, Loughborough, Leisc. LE11 5RH (GB).  KINDON, Nicholas [GB/GB]; AstraZeneca, R &amp; D Charn-  wood, Bakewell Road, Loughborough, Leisc. LE11 5RH  (GB). MCINALLY, Thomas [GB/GB]; AstraZeneca, R &amp;  D Charnwood, Bakewell Road, Loughborough, Leisc. LE11  5RH (GB). ROBERTS, Bryan [GB/GB]; AstraZeneca, R</p> </td> <td style="width: 50%; vertical-align: top;"> <p>&amp; D Charnwood, Bakewell Road, Loughborough, Leisc.  LE11 5RH (GB). THOM, Stephen [GB/GB]; AstraZeneca,  R &amp; D Charnwood, Bakewell Road, Loughborough, Leisc.  LE11 5RH (GB).</p> <p>(74) Agent: ASTRAZENECA AB; Global Intellectual Property,  Patents, S-151 85 Södertälje (SE).</p> <p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB,  BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM,  DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,  IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,  LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,  RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,  UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH,  GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian  patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,  IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF,  CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.  Before the expiration of the time limit for amending the  claims and to be republished in the event of the receipt of  amendments.</i></p> </td> </tr> </table>			<p>(21) International Application Number: PCT/SE00/00563</p> <p>(22) International Filing Date: 22 March 2000 (22.03.00)</p> <p>(30) Priority Data:  9901117-3                      26 March 1999 (26.03.99)                      SE  9902194-1                      10 June 1999 (10.06.99)                      SE</p> <p>(71) Applicant (for all designated States except MG US): AS-  TRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate,  London W1Y 6LN (GB).</p> <p>(71) Applicant (for MG only): ASTRAZENECA AB [SE/SE];  S-151 85 Södertälje (SE).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BAXTER, Andrew  [GB/GB]; AstraZeneca, R &amp; D Charnwood, Bakewell  Road, Loughborough, Leisc. LE11 5RH (GB). BROUGH,  Stephen [GB/GB]; AstraZeneca, R &amp; D Charnwood,  Bakewell Road, Loughborough, Leisc. LE11 5RH (GB).  KINDON, Nicholas [GB/GB]; AstraZeneca, R &amp; D Charn-  wood, Bakewell Road, Loughborough, Leisc. LE11 5RH  (GB). MCINALLY, Thomas [GB/GB]; AstraZeneca, R &amp;  D Charnwood, Bakewell Road, Loughborough, Leisc. LE11  5RH (GB). ROBERTS, Bryan [GB/GB]; AstraZeneca, R</p>	<p>&amp; D Charnwood, Bakewell Road, Loughborough, Leisc.  LE11 5RH (GB). THOM, Stephen [GB/GB]; AstraZeneca,  R &amp; D Charnwood, Bakewell Road, Loughborough, Leisc.  LE11 5RH (GB).</p> <p>(74) Agent: ASTRAZENECA AB; Global Intellectual Property,  Patents, S-151 85 Södertälje (SE).</p> <p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB,  BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM,  DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,  IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,  LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,  RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,  UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH,  GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian  patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,  IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF,  CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.  Before the expiration of the time limit for amending the  claims and to be republished in the event of the receipt of  amendments.</i></p>
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<p>(54) Title: NOVEL COMPOUNDS</p> <div style="text-align: center; margin: 20px 0;"> <math display="block">R^1 - (Q)_m - T - (CR^2R^3)_n - V - \text{C}_6\text{H}_{10} - W - X - R^4 \quad (I)</math> </div> <p>(57) Abstract</p> <p>The invention provides compounds of general formula (I) wherein: R<sup>1</sup> represents optionally substituted C<sub>1</sub>-C<sub>12</sub> alkyl or optionally substituted 3- to 10-membered saturated or unsaturated ring system comprising up to two ring carbon atoms that form carbonyl groups and comprising up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur; m is 0-1; Q represents OCH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkylene or C<sub>2</sub>-C<sub>4</sub> alkenylene; T represents C(O)NH, or when m is 0, T may additionally represent a bond or NH, or when m is 1 and Q represents C<sub>1</sub>-C<sub>4</sub> alkylene, T may additionally represent NH; n is 1-4; each R<sup>2</sup> and R<sup>3</sup> independently represents H or C<sub>1</sub>-C<sub>4</sub> alkyl; V represents N, and W represents N or CH; X represents O, C(O), CH(OH), SO<sub>2</sub>, NH or N(C<sub>1</sub>-C<sub>6</sub> alkyl), provided that when W represents N, then X represents either C(O) or SO<sub>2</sub> and when W represents CH, then X is other than SO<sub>2</sub>; R<sup>4</sup> represents optionally substituted phenyl; R<sup>5</sup> and R<sup>6</sup> each independently represent H, C<sub>1</sub>-C<sub>6</sub> alkyl or hydroxyC<sub>1</sub>-C<sub>6</sub> alkyl, or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring; R<sup>7</sup> and R<sup>8</sup> each independently represent H or C<sub>1</sub>-C<sub>6</sub> alkyl; and R<sup>9</sup> represents OH or -NR<sup>7</sup>R<sup>8</sup>; processes for their preparation, pharmaceutical compositions containing them and their use in therapy.</p>				

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## NOVEL COMPOUNDS

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

5

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved  
10 four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

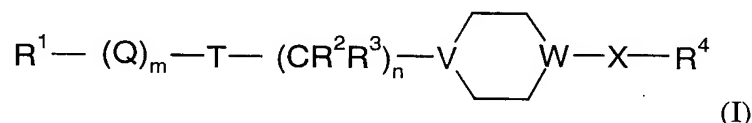
15 The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and  
20 MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 $\alpha$  and 1 $\beta$  (MIP-1 $\alpha$  and MIP-1 $\beta$ ).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2,  
25 CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Certain piperidinyl derivatives and piperazinyl derivatives are known from U.S. Patents Nos. 3 787 419, 4 559 349 and 5 210 086 for use respectively as central nervous system depressants, antipsychotic agents and as  $\alpha_1$ -adrenoreceptor antagonists.

- 5 In accordance with the present invention, there is therefore provided a compound of general formula



wherein:

- 10  $R^1$  represents a  $C_1$ - $C_{12}$  alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylthio and  $C_1$ - $C_6$  alkoxycarbonyl groups, or
- $R^1$  represents a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise
- 15 up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one or more substituents independently selected from halogen atoms, and cyano, nitro, hydroxyl,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxycarbonyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy,  $-NR^5R^6$ ,  $C_3$ - $C_6$  cycloalkylamino,  $C_1$ - $C_6$  alkylthio,  $C_1$ - $C_6$  alkylthio $C_1$ - $C_6$  alkyl,
- 20  $C_1$ - $C_6$  alkylcarbonylamino,  $-C(O)NR^7R^8$ , sulphonamido ( $-SO_2NH_2$ ), (di) $C_1$ - $C_6$  alkylsulphonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and  $C(O)R^9$ -substituted  $C_1$ - $C_6$  alkyl or  $C_1$ - $C_6$  alkoxy groups;
- $m$  is 0 or 1;
- 25  $Q$  represents a group  $OCH_2$ ,  $C_1$ - $C_4$  alkylene or  $C_2$ - $C_4$  alkenylene;
- $T$  represents a group  $C(O)NH$ , or when  $m$  is 0,  $T$  may additionally represent a bond or a group  $NH$ , or when  $m$  is 1 and  $Q$  represents  $C_1$ - $C_4$  alkylene,  $T$  may additionally represent a group  $NH$ ;



n is 1, 2, 3 or 4;

each  $R^2$  independently represents a hydrogen atom or a  $C_1$ - $C_4$  alkyl group;

each  $R^3$  independently represents a hydrogen atom or a  $C_1$ - $C_4$  alkyl group;

V represents a nitrogen atom;

5 W represents a nitrogen atom or a group CH;

X represents an oxygen atom or a group C(O), CH(OH), NH or N( $C_1$ - $C_6$  alkyl),

provided that when W represents a nitrogen atom, then X represents C(O);

$R^4$  represents a phenyl group optionally substituted by one or more substituents independently selected from halogen atoms, and amino, nitro, cyano, sulphonyl ( $-SO_3H$ ),

10 sulphonamido ( $-SO_2NH_2$ ),  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy and  $C_1$ - $C_6$  alkylsulphonyl groups;

$R^5$  and  $R^6$  each independently represent a hydrogen atom or a  $C_1$ - $C_6$  alkyl or hydroxy $C_1$ - $C_6$  alkyl group, or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring;

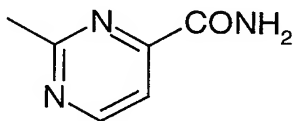
15  $R^7$  and  $R^8$  each independently represent a hydrogen atom or a  $C_1$ - $C_6$  alkyl group; and  $R^9$  represents a hydroxyl or  $-NR^7R^8$  group;

with the provisos that

(a) when m is 0, T is CONH, n is 2, 3 or 4 and each  $R^2$  and  $R^3$  represents hydrogen, W is CH, X is C(O) or CH(OH) and  $R^1$  represents a substituted 3- to 10-membered unsaturated ring system, then the one or more substituents in the ring system do not include hydroxyl, halogen,  $C_1$ - $C_6$  alkoxy or  $C_1$ - $C_6$  haloalkoxy, and

(b) when W is N, X is C(O),  $R^4$  represents 3-trifluoromethylphenyl, m is 0 and T is a bond, then  $R^1$  and  $(CR^2R^3)_n$  taken together do not represent a  $C_1$ - $C_6$  alkyl group, and

(c) when W is CH, X is O, n is 2 or 3 and each  $R^2$  and  $R^3$  represents hydrogen, m is 0 and  
25 T is NH, then  $R^1$  does not represent a group



or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Further, the alkyl moieties in a dialkylamino, di(hydroxyalkyl)amino or dialkylsulphonamido substituent group may be the same or  
 5 different.

$R^1$  represents a  $C_1$ - $C_{12}$ , preferably  $C_1$ - $C_{10}$ , alkyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from cyano, hydroxyl,  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy,  
 10 pentoxy or hexoxy),  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , alkylthio (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylthio) and  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , alkoxycarbonyl (e.g. methoxy-, ethoxy-, propoxy-, butoxy-, pentoxy- or hexoxycarbonyl) groups, or

$R^1$  represents a 3- to 10-membered saturated or unsaturated ring system comprising up to two ring carbon atoms that form carbonyl groups and comprising up to 4 ring heteroatoms  
 15 independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen atoms (fluorine, chlorine, bromine or iodine), and cyano, nitro, hydroxyl,  $C_1$ - $C_6$  alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl or hexyl),  $C_3$ - $C_6$  cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl),  
 20  $C_1$ - $C_6$  alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy),  $C_1$ - $C_6$  alkoxycarbonyl (e.g. methoxy-, ethoxy-, propoxy-, butoxy-, pentoxy- or hexoxycarbonyl),  $C_1$ - $C_6$  haloalkyl (e.g. trifluoromethyl),  $C_1$ - $C_6$  haloalkoxy (e.g. trifluoromethoxy),  $-NR^5R^6$ ,  $C_3$ - $C_6$  cycloalkylamino (cyclopropyl-, cyclobutyl-, cyclopentyl- or cyclohexylamino),  $C_1$ - $C_6$  alkylthio (e.g. methyl-, ethyl-, propyl-, butyl-,  
 25 pentyl- or hexylthio),  $C_1$ - $C_6$  alkylthio $C_1$ - $C_6$  alkyl (e.g. methylthiomethyl),  $C_1$ - $C_6$  alkylcarbonylamino (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylcarbonylamino),  $-C(O)NR^7R^8$ , sulphonamido ( $-SO_2NH_2$ ), (di) $C_1$ - $C_6$  alkylsulphonamido (e.g. (di)methylsulphonamido or (di)ethylsulphonamido), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl,

furanyl, and  $C(O)R^9$ -substituted  $C_1$ - $C_6$  alkyl or  $C_1$ - $C_6$  alkoxy groups, the alkyl and alkoxy moieties being as defined above.

The 3- to 10-membered saturated or unsaturated ring system in the group  $R^1$  may be  
5 monocyclic, or polycyclic comprising 2 or more fused rings, examples of which include cyclobutyl, cyclopentyl, cyclohexyl, norbornylenyl, adamantyl, piperidyl, phenyl, naphthyl, naphthyridinyl, 1,3-benzodioxolyl, pyrazolyl, furanyl, pyridyl, thienyl, benzoxazolyl, benzothiazolyl, chromonyl, imidazolyl, quinoliny, isoquinoliny, benzimidazolyl, pyrimidinyl, pyrazolopyrimidinyl, thienopyrimidinyl,  
10 thiazolopyrimidinyl, pyrimidinedione, pyrazinyl, pyridazinyl, purinyl, quinoxaliny, thiazolyl, isothiazolyl and 2,4-dioxo-3,4-dihydro-quinazolinyl.

Preferably,  $R^1$  represents a  $C_1$ - $C_{10}$  alkyl group optionally substituted by one or two substituents independently selected from cyano, hydroxyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio  
15 and  $C_1$ - $C_4$  alkoxycarbonyl groups, or  
 $R^1$  represents a 3- to 10-membered saturated or unsaturated ring system comprising up to two ring carbon atoms that form carbonyl groups and comprising up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one, two or three substituents independently selected from halogen atoms,  
20 and cyano, nitro, hydroxyl,  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkoxycarbonyl,  $C_1$ - $C_3$  haloalkyl,  $C_1$ - $C_3$  haloalkoxy,  $-NR^5R^6$ ,  $C_3$ - $C_6$  cycloalkylamino,  $C_1$ - $C_4$  alkylthio,  $C_1$ - $C_4$  alkylthio- $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkylcarbonylamino,  $-C(O)NR^7R^8$ , phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and  $C(O)R^9$ -substituted  $C_1$ - $C_4$  alkyl or  
25  $C_1$ - $C_4$  alkoxy groups.

Preferably Q represents a group  $OCH_2$ ,  $C_1$ - $C_3$  alkylene or  $C_2$ - $C_3$  alkenylene.

Each  $R^2$  independently represents a hydrogen atom or a  $C_1$ - $C_4$  alkyl (e.g. methyl, ethyl,  
30 propyl, isopropyl or butyl) group, and is especially a hydrogen atom.

Each  $R^3$  independently represents a hydrogen atom or a  $C_1$ - $C_4$  alkyl (e.g. methyl, ethyl, propyl, isopropyl or butyl) group, and is especially a hydrogen atom.

5 Preferably n is 2 or 3.

X preferably represents an oxygen atom or a group  $C(O)$  or  $NH$ .

$R^4$  represents a phenyl group optionally substituted by one or more (e.g. one, two, three or  
10 four) substituents independently selected from halogen atoms (fluorine, chlorine, bromine or iodine), and amino, nitro, cyano, sulphonyl ( $-SO_3H$ ), sulphonamido ( $-SO_2NH_2$ ),  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl),  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , haloalkyl (e.g. trifluoromethyl),  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , haloalkoxy (e.g. trifluoromethoxy) and  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , alkylsulphonyl (e.g. methyl-, ethyl-,  
15 propyl-, butyl-, pentyl- or hexylsulphonyl) groups.

Preferably,  $R^4$  represents a phenyl group optionally substituted by one or two halogen atoms, particularly chlorine atoms.

20  $R^5$  and  $R^6$  each independently represent a hydrogen atom or a  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , alkyl or hydroxy $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , alkyl group, or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring. The alkyl moiety in each case may, for example, be a methyl, ethyl, propyl, butyl, pentyl or hexyl group. In the hydroxyalkyl group, the hydroxyl group may be attached to  
25 any suitable carbon atom of the alkyl moiety.

$R^7$  and  $R^8$  each independently represent a hydrogen atom or a  $C_1$ - $C_6$ , preferably  $C_1$ - $C_4$ , alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl) group. Preferably,  $R^7$  and  $R^8$  each independently represent a hydrogen atom or a methyl group.

R<sup>9</sup> represents a hydroxyl or, preferably, -NR<sup>5</sup>R<sup>6</sup> group.

Examples of particularly preferred compounds of the invention include:

- 4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-ethoxybenzamide hydrochloride,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-isopropoxybenzamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-ethoxybenzamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide hydrochloride,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethoxy)benzamide hydrochloride,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide hydrochloride,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide hydrochloride,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride,
- 3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide hydrochloride,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide hydrochloride,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-hydroxybenzamide hydrochloride,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-[2-(methylamino)-2-oxoethoxy]benzamide hydrochloride,
- 2-[3-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl}-2,4-dioxo-3,4-dihydro-1(2H)-quinazolinyl]-N,N-dimethylacetamide hydrochloride,
- N-{2-[4-(3,4-Dichlorobenzoyl)-1-piperazinyl]ethyl}-3-methoxybenzamide hydrochloride,
- 3,4-Dichloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}benzamide,
- 4-Chloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide hydrochloride,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-9-methyl-9H-purin-6-amine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzothiazol-2-amine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzoxazol-2-amine,  
6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrazinamine,  
5 6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-pyridazinamine,  
6-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-1,3-dimethyl-2,4(1H,3H)-  
pyrimidinedione,  
N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-4-methyl-  
benzamide, hydrochloride salt,  
10 N-{1-[4-(3,4-Dichloro-phenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-methoxy-  
benzamide, hydrochloride salt,  
N-{2-[4-(3,4-Dichloroanilino)-1-piperidinyl]ethyl}-3-methoxybenzamide dihydrochloride,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-(3-methoxybenzyl)amine  
dihydrochloride,  
15 3-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methoxy-2,4(1H,3H)-  
quinazolinedione,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-nitrobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methylbenzamide,  
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-dinitrobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-iodobenzamide,  
4-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
4-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
30 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methylbenzamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-nitrobenzamide,  
3-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
3,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide,  
5 2,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methylbenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-iodobenzamide,  
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-nitrobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide,  
10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-5-  
(trifluoromethyl)benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide,  
3,5-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)benzamide,  
15 3-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
2-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide,  
3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
2-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-difluorobenzamide,  
2,3-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-naphthamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-6-  
25 (trifluoromethyl)benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-difluorobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-thiophenecarboxamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide,  
Methyl 4-({2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}amino)-4-oxobutanoate,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclobutanecarboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxyacetamide,
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclohexanecarboxamide,
- (E)-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide,
- 2-Chloro-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}nicotinamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclopentanecarboxamide,
- 10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenoxyacetamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}benzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide,
- 4-(tert-Butyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}benzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methylbenzamide,
- 15 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-nitrobenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-methylbenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-cyanobenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-furamide,
- 20 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-nitrobenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-naphthamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(2,3-dihydro-1,4-benzodioxin-2-yl)-1,3-thiazole-4-carboxamide,
- 25 N-2~-Cyclopropyl-N-4~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine,
- 2-{[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-pyrimidinyl]amino}-1-ethanol,
- 2-{[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-pyrimidinyl](methyl)amino}-1-ethanol,
- 30



- N-4--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-2~-phenyl-2,4-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)-4-pyrimidinamine,
- N-4--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2,4-pyrimidinediamine,
- 5 N-4--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-2~,6-dimethyl-2,4-pyrimidinediamine,
- 2-Chloro-N-4~-cyclopropyl-N-6--{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenyl-2-pyrimidinamine,
- 10 N-2--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-4~,N-4~,6-trimethyl-2,4-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(propylsulfanyl)-2-pyrimidinamine,
- 15 N-2--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-4~-phenyl-2,4-pyrimidinediamine,
- N-4~-Cyclopropyl-N-2--{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}[1,8]naphthyridin-2-amine,
- 20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-pyridinyl)-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-dimethoxy-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-furyl)-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1-methyl-1H-pyrazolo[3,4-
- 25 d]pyrimidin-4-amine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-purin-6-amine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methylthieno[2,3-d]pyrimidin-4-amine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methylthieno[3,2-d]pyrimidin-4-
- 30 amine,

- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-thiophenecarboxamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}cyclohexanecarboxamide,  
 5 (E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-phenoxyacetamide,  
 (E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(4-nitrophenyl)-2-propenamide,  
 2-(1-Adamantyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}acetamide,  
 (4-Chlorophenyl)(1-{2-[(2-fluoro-4,5-dimethoxybenzyl)amino]ethyl}-4-  
 10 piperidinyl)methanone,  
 (4-Chlorophenyl)(1-{2-[(3,4,5-trimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,  
 (4-Chlorophenyl)(1-{2-[(3-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
 (4-Chlorophenyl){1-[2-(isobutylamino)ethyl]-4-piperidinyl}methanone,  
 4-[(1-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-4-ethylhexanenitrile,  
 15 (4-Chlorophenyl)(1-{2-[(7-hydroxy-3,7-dimethyloctyl)amino]ethyl}-4-  
 piperidinyl)methanone,  
 (4-Chlorophenyl)[1-(2-{[(6-nitro-1,3-benzodioxol-5-yl)methyl]amino}ethyl)-4-  
 piperidinyl]methanone,  
 [1-(2-{[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}ethyl)-4-piperidinyl](4-  
 20 chlorophenyl)methanone,  
 (4-Chlorophenyl)[1-(2-{[3-nitro-4-(2-pyridinylsulfanyl)benzyl]amino}ethyl)-4-  
 piperidinyl]methanone,  
 (4-Chlorophenyl)[1-(2-{[(E)-3-(4-nitrophenyl)-2-propenyl]amino}ethyl)-4-  
 piperidinyl]methanone,  
 25 (4-Chlorophenyl){1-[2-({[5-(3-nitrophenyl)-2-furyl]methyl}amino)ethyl]-4-  
 piperidinyl}methanone,  
 (4-Chlorophenyl)[1-(2-{[5-nitro-2-(2-pyridinylsulfanyl)benzyl]amino}ethyl)-4-  
 piperidinyl]methanone,  
 6-[(1-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-2-  
 30 (methylsulfanyl)nicotinonitrile,

- {1-[2-({[5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}amino)ethyl]-4-piperidinyl}(4-chlorophenyl)methanone,  
(4-Chlorophenyl)[1-(2-{[3-(methylsulfanyl)butyl]amino}ethyl)-4-piperidinyl]methanone,  
(4-Chlorophenyl)[1-(2-{[(4-phenyl-4-piperidinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
5 piperidinyl]methanone,  
(4-Chlorophenyl)[1-(2-{[(1-phenyl-1H-pyrazol-5-yl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
Ethyl 3-[(2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl)-amino)methyl]cyclohexanecarboxylate,  
10 N-{4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]phenyl}acetamide,  
(4-Chlorophenyl)(1-{2-[(2,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
(4-Chlorophenyl)(1-{2-[(4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
(4-Chlorophenyl)(1-{2-[(2,6-dichlorobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
(4-Chlorophenyl)(1-{2-[(2-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone,  
15 (4-Chlorophenyl)[1-(2-{[(3-methyl-2-thienyl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
(4-Chlorophenyl)(1-{2-[(3-hydroxy-4-methoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,  
3-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4H-chromen-4-one,  
20 [1-(2-{[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone,  
(4-Chlorophenyl)[1-(2-{[(2,6-dichloro-4-pyridinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
(4-Chlorophenyl)[1-(2-{[(2-phenyl-1H-imidazol-4-yl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
25 piperidinyl]methanone,  
(4-Chlorophenyl)[1-(2-{[(5-ethyl-2-thienyl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
(4-Chlorophenyl)[1-(2-{[(2-chloro-3-quinolinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
(4-Chlorophenyl)[1-(2-{[(6-methyl-2-pyridinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
30 piperidinyl]methanone,

- (4-Chlorophenyl)(1-{2-[(3-quinolinylmethyl)amino]ethyl}-4-piperidinyl)methanone,  
4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-1,5-dimethyl-2-phenyl-  
1,2-dihydro-3H-pyrazol-3-one,  
(4-Chlorophenyl)(1-{2-[(4-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone,  
5 (4-Chlorophenyl)(1-{2-[(3-hydroxy-4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
(4-Chlorophenyl)(1-{2-[(3,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
(1-{2-[(2-Chloro-6-fluorobenzyl)amino]ethyl}-4-piperidinyl)(4-chlorophenyl)methanone,  
[1-(2-[(4-Bromo-1H-pyrazol-3-yl)methyl]amino)ethyl]-4-piperidinyl(4-  
chlorophenyl)methanone,  
10 3-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-6,7-dimethyl-4H-  
chromen-4-one,  
2-{2-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4-nitrophenoxy}acetic  
acid,  
(4-Chlorophenyl)[1-(2-[(1-methyl-1H-benzimidazol-2-yl)methyl]amino)ethyl]-4-  
15 piperidinyl)methanone,  
(4-Chlorophenyl)[1-(2-[(2,4-dimethoxy-5-pyrimidinyl)methyl]amino)ethyl]-4-  
piperidinyl)methanone,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(methylamino)benzamide,  
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,  
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxy-4-methylbenzamide,  
3-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzodioxole-5-carboxamide,  
4-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluoro-4-methoxybenzamide,  
25 5-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methyl-2-furamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,5-dimethyl-2-furamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-ethoxy-1-benzofuran-2-  
carboxamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-1-benzofuran-2-carboxamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methoxy-1-benzofuran-2-carboxamide,  
5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-fluorophenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methylphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methylphenyl)acetamide,  
2-(3-Bromophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
10 2-(2-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
2-(4-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(trifluoromethyl)phenyl]acetamide,  
2-(3-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dimethoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dichlorophenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-fluoro-4-methoxyphenyl)acetamide,  
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-ethoxyphenyl)acetamide,  
2-(1,3-Benzodioxol-5-yl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[4-(dimethylamino)phenyl]acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methylphenyl)acetamide,  
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-difluorophenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenylbutanamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenylpropanamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(3-methoxyphenyl)propanamide,  
30 2-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-carboxamide,

- 2-(Acetylamino)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-pyridinyl)-1,3-thiazole-4-carboxamide,
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-dimethyl-1,3-thiazole-5-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,5-dimethyl-1,3-oxazole-4-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-imidazole-4-carboxamide,
- 10 N-{2-[4-(3,4-Chlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide, hydrochloride salt,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2,6-dimethoxy-4-pyrimidinamine,
- 15 N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-6-
- 20 (trifluoromethyl)-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine,
- 25 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-methyl-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(ethylsulfanyl)-6-methyl-4-pyrimidinamine,
- N~2~-Cyclopropyl-N~4~-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2,4-
- 30 pyrimidinediamine,

- 2-{{4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl} amino)-2-pyrimidinyl} amino}-1-ethanol,
- 2-[[4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl} amino)-2-pyrimidinyl](methyl)amino]-1-ethanol,
- 5 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-4-pyrimidinamine,
- N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2,4-pyrimidinediamine,
- N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,6-dimethyl-2,4-pyrimidinediamine,
- 10 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-phenyl-2-pyrimidinamine,
- N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-fluoro-2,4-pyrimidinediamine,
- N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine,
- 15 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(trifluoromethyl)-2-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(propylsulfanyl)-2-pyrimidinamine,
- N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~-phenyl-2,4-pyrimidinediamine,
- 20 N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,6-dimethyl-2,4-pyrimidinediamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}[1,8]naphthyridin-2-amine,
- 2-{{2-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl} amino)-4-pyrimidinyl} amino}-1-ethanol,
- 25 2-[[2-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl} amino)-4-pyrimidinyl](methyl)amino]-1-ethanol,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-pyridinyl)-2-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-thienyl)-2-pyrimidinamine,
- 30 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrimidinamine,

- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4,6-dimethoxy-2-pyrimidinamine,  
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-furyl)-2-pyrimidinamine,  
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(2-thienyl)-2-pyrimidinamine,  
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1H-purin-6-amine,  
5 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methylthieno[2,3-d]pyrimidin-4-amine,  
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-7-methylthieno[3,2-d]pyrimidin-4-amine,  
N~7~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methyl[1,3]thiazolo[4,5-  
10 d]pyrimidine-2,7-diamine,  
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-9-methyl-9H-purin-6-amine,  
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,  
5-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,  
6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,  
15 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-pyridinamine,  
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzothiazol-2-amine,  
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzoxazol-2-amine,  
6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrazinamine,  
6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-3-pyridazinamine,  
20 6-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,6-dimethoxy-4-pyrimidinamine,  
N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine,  
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2-(methylsulfanyl)-4-  
30 pyrimidinamine,



N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-methyl-4-pyrimidinamine, and

N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-N~2~-phenyl-2,4-pyrimidinediamine.

5

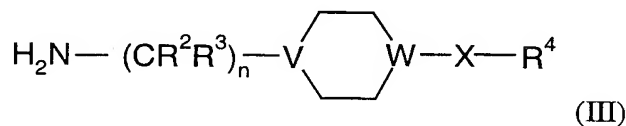
The present invention further provides a process for the preparation of a compound of formula (I) which comprises

(i) when T represents a group C(O)NH, reacting a compound of general formula



10

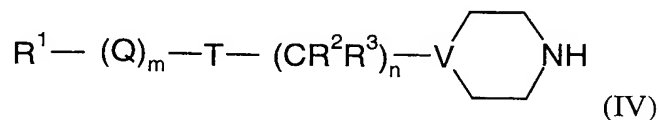
wherein  $L^1$  represents a leaving group (e.g. a hydroxyl or halide, such as chloride, group) and  $R^1$ , m and Q are as defined in formula (I), with a compound of general formula



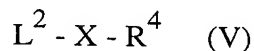
15 or an acid addition salt thereof (e.g. trifluoroacetate) wherein n,  $R^2$ ,  $R^3$ , V, W, X and  $R^4$  are as defined in formula (I); or

(ii) when T represents a group C(O)NH and W represents a nitrogen atom, reacting a compound of general formula

20

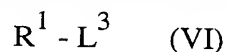


wherein  $R^1$ , m, Q, T, n,  $R^2$ ,  $R^3$  and V are as defined in formula (I), with a compound of general formula



25 wherein  $L^2$  represents a leaving group (e.g. a halogen atom) and X and  $R^4$  are as defined in formula (I); or

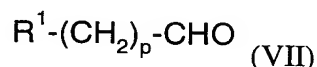
(iii) when T represents a group NH and m is 0, reacting a compound of general formula



wherein  $L^3$  represents a leaving group (e.g. a halogen atom) and  $R^1$  is as defined in formula (I), with a compound of formula (III) as defined in (i) above; or

5

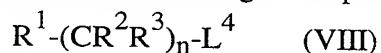
(iv) when T represents a group NH, m is 1 and Q represents  $C_1$ - $C_4$  alkylene, reacting a compound of general formula



wherein p is 0, 1, 2 or 3 and  $R^1$  is as defined in formula (I), with a compound of formula (III) as defined in (i) above; or

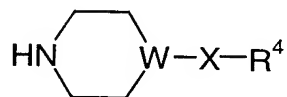
10

(v) when T represents a bond and m is 0, reacting a compound of general formula



wherein  $L^4$  represents a leaving group such as a halogen atom (e.g. chlorine) and n,  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I), with a compound of general formula

15



(IX)

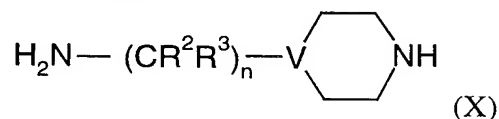
20 wherein W, X and  $R^4$  are as defined in formula (I);

and optionally after (i), (ii), (iii), (iv) or (v) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

25

The processes of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as dimethylformamide or dichloromethane at a temperature of, for example, 15°C or above such as a temperature in the range from 20 to 100°C.

Compounds of formula (III) in which W represents a nitrogen atom may be prepared by reacting a compound of general formula



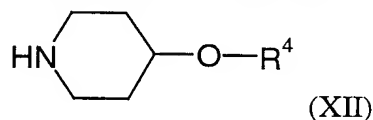
in which n,  $\text{R}^2$ ,  $\text{R}^3$  and V are as defined in formula (I) with a compound of formula (V) as  
5 defined above.

Compounds of formula (X) can be prepared by reacting piperazine with a compound of general formula



wherein  $\text{L}^5$  represents a halogen atom such as a bromine atom and n,  $\text{R}^2$  and  $\text{R}^3$  are as defined in formula (I).

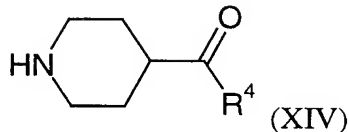
Compounds of formula (III) in which W represents a group CH and X represents an oxygen  
15 atom may be prepared by reacting a compound of general formula



in which  $\text{R}^4$  is as defined in formula (I), with a compound of formula (XI).

Compounds of formula (XII) may be prepared by reacting 4-piperidinol with a compound  
20 of general formula (XIII),  $\text{R}^4-\text{OH}$ , wherein  $\text{R}^4$  is as defined in formula (I), in the presence of a coupling agent such as diethyl azodicarboxylate and triphenylphosphine and in a solvent such as benzene or tetrahydrofuran at a temperature typically in the range from 20 to 30 °C.

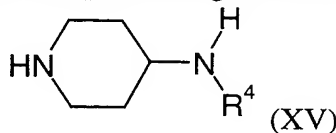
25 Compounds of formula (III) in which W represents a group CH and X represents a group C(O) may be prepared by reacting a compound of general formula



wherein  $R^4$  is as defined in formula (I), with a compound of formula (XI).

Compounds of formula (III) in which W represents a group CH and X represents a group  
 5 CH(OH) may be prepared by reducing/hydrogenating a corresponding compound of  
 formula (III) in which X represents C(O) using techniques known in the art.

Compounds of formula (III) in which W represents a group CH and X represents a group  
 NH may be prepared by reacting a compound of general formula



10

in which  $R^4$  is as defined in formula (I), with a compound of formula (XI).

Compounds of formula (XV) may be prepared by reacting 4-piperidone with a compound  
 of general formula (XVI),  $R^4-NH_2$ , wherein  $R^4$  is as defined in formula (I), in the presence  
 15 of a reducing agent such as sodium cyanoborohydride or sodium borohydride and in a  
 solvent such as methanol or benzene at a temperature typically in the range from  
 20 to 90 °C.

Compounds of formula (III) in which W represents a group CH and X represents a group  
 20  $N(C_1-C_6 \text{ alkyl})$  may be prepared by alkylating a corresponding compound of formula (III)  
 in which X represents a group NH, using techniques conventional in the art.

Compounds of formula (IV) may be prepared by reacting a compound of formula (II) with  
 a compound of formula (X).

25

Compounds of formulae II, V, VI, VII, VIII, IX, XI, XIII, XIV and XVI are either commercially available, are well known in the literature or may be prepared easily using known techniques.

- 5 Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. For example, compounds of formula (I) in which  $R^1$  represents an alkoxy-substituted phenyl group can be converted to compounds of formula (I) in which  $R^1$  represents a hydroxy-substituted phenyl group by reaction with boron tribromide in a solvent such as dichloromethane. Further, compounds of formula (I) in which X represents  
10 C(O) can be converted to compounds of formula (I) in which X represents CH(OH) by reaction with triethylsilane and trifluoroacetic acid in a solvent such as dichloromethane.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting  
15 reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in  
20 Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable  
25 salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will  
30 be understood that the invention encompasses the use of all geometric and optical isomers

of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR1 and/or CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

Examples of these conditions are:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopic dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) (**gastrointestinal tract**) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

5 (5) (**other tissues and systemic disease**) multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, Sezary syndrome and idiopathic thrombocytopenia purpura; and

10 (6) (**allograft rejection**) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

15 Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the  
20 manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

25 The invention also provides a method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

- 5 The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably  
10 comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound  
15 of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a  
20 pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

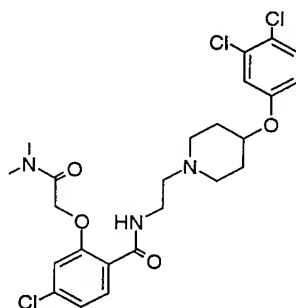
The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols  
25 and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.



The invention will now be further explained by reference to the following illustrative examples.

### Example 1

5 **4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide**



(i) **tert-Butyl 4-(3,4-dichlorophenoxy)-1-piperidinecarboxylate**

Diethyl azodicarboxylate (12.6ml) was added to a solution of triphenylphosphine (20.8g) in tetrahydrofuran (300ml) at 0° C. After 15 minutes 3,4-dichlorophenol (12.9g) was added, after a further 10 minutes tert-butyl 4-hydroxy-1-piperidinecarboxylate (14.5g) in tetrahydrofuran (100ml) was added dropwise over 0.5 hour. The solution was stirred at room temperature for 5 hours and concentrated to a small volume. The residue was partitioned between ether and brine. The organic phase was separated, dried and evaporated to a gum. Purification by chromatography (ethyl acetate : isohexane 95:5) gave the sub-titled product as an oil (20g).

MS: APCI(+ve): 246 (M-BOC+2H)

20 (ii) **4-(3,4-Dichlorophenoxy)piperidine**

The product from step (i) was dissolved in dichloromethane (200ml) and trifluoroacetic acid (100ml) was added. After 18 hours at room temperature the solution was evaporated and the resultant gum triturated under ether to give the sub-titled product as a solid (16.2g).

25 (iii) **tert-Butyl 2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethylcarbamate**

The product from step (ii) (6.55g) was dissolved in DMF (50ml) and triethylamine (7.9ml) was added. tert-Butyl 2-bromoethylcarbamate (4.3 g) in DMF (5ml) was added and the solution stirred at room temperature for 3 days. Ethyl acetate and water were added, the organic phase separated, dried and evaporated to a gum. Purification by chromatography (dichloromethane : methanol 95:5) gave the sub-titled product as a gum (5.7g).

MS: APCI(+ve): 389(M+H)

**(iv) 2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethylamine trifluoroacetate**

The product from step (iii) was dissolved in dichloromethane (200ml) and trifluoroacetic acid (100ml) added. After 18hrs at room temperature the solvent was evaporated and the resultant gum triturated under ether to give the sub-titled product as a solid (5.7g).

MS: APCI(+ve): 290(M+H)

**(v) 2-(Dimethylamino)-2-oxoethyl 4-chloro-2-[2-(dimethylamino)-2-oxoethoxy]benzoate**

A mixture of 4-chloro-2-hydroxybenzoic acid (5g),  $\text{Cs}_2\text{CO}_3$  (17.5g) and 2-chloro-N,N-dimethylacetamide (6.6g) was stirred and heated at 70 °C for 3 hours. Water and ethyl acetate were added, the organic phase separated, dried and concentrated to a gum which was purified by chromatography (ethyl acetate : methanol, 9:1) to give the sub-titled product as a solid (8.0g).

MS: APCI(+ve) 343(M+H)

Melting point: 140-141 °C

**(vi) 4-Chloro-2-[2-(dimethylamino)-2-oxoethoxy]benzoic acid**

The product from step (v) (1.0g) was dissolved in a 2 : 1 water : methanol mixture (15ml) and  $\text{LiOH}\cdot\text{H}_2\text{O}$  added. After 2 hours 2M aqueous HCl solution and ethyl acetate were

added, the organic phase separated, dried and concentrated to give the sub-titled product as a solid (1.2g).

MS: APCI(+ve) 258(M+H)

5 Melting point: 141-142 °C

**(vii) 4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide**

The product from step (vi) (0.3g) and N,N-carbonyldiimidazole (0.19g) were dissolved in  
10 DMF (20ml) and the solution stirred at room temperature for 1 hour. The product from step (iv) (0.42g) and triethylamine (0.32ml) were added. After 20 hours water and ether were added, the organic phase separated, dried and concentrated to a gum which was purified by chromatography (dichloromethane : methanol, 93:7) to give the titled product as a solid (0.38g).

15

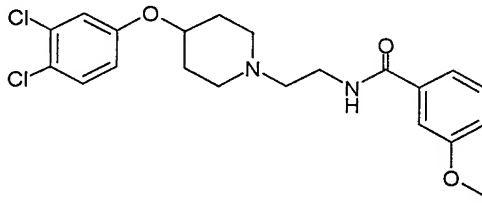
MS: ESI 528.12 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 9.17 (t, 1H), 7.88 (d, 1H), 7.48 (d, 1H), 7.38 (d, 1H), 7.24 (d, 1H), 7.13 (dd, 1H), 6.99 (dd, 1H), 5.11 (s, 2H), 4.32 (m, 1H), 3.42 (m, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.73 (m, 2H), 2.50 (m, 2H), 2.30 (m, 2H), 1.90 (m, 2H), 1.59 (m, 2H).

20 Melting point: 139-40 °C

**Example 2**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-ethoxybenzamide hydrochloride**



25

The product of Example 1 step (iv) (0.4g) was dissolved in DMF (10ml), PyBrop (0.541g), 3-ethoxybenzoic acid (0.167g) and N,N-di-isopropylethylamine (0.5g) were added. After

18 hours at room temperature chloroform and aqueous NaHCO<sub>3</sub> solution were added. The organic phase was separated, dried and concentrated to leave a gum which was purified by chromatography ( ethyl acetate : methanol 97:3) to give an oil. Addition of 1.0M ethereal hydrogen chloride solution gave the titled product as a solid (0.14g).

5

MS: ESI 437.14 (M+H)

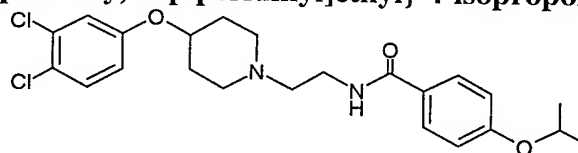
<sup>1</sup>H NMR: δ(DMSO) 8.87 (bs, 1H), 7.50 (m, 3H), 7.40 (m, 2H), 7.06 (m, 2H), 4.83 / 4.62 (m, 1H ), 4.08 (q, 2H), 3.67 (m, 3H), 3.47 (m, 1H), 3.17 (m, 3H), 2.20 (m, 2H), 2.03 (m, 2H), 1.34 (t, 3H)

10 

Melting point: 191-193 °C

### Example 3

#### N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-isopropoxybenzamide

15 

Prepared by the same method as Example 2 using 4-isopropoxybenzoic acid without the addition of 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid (0.12g).

MS: ESI 451.14 (M+H)

20 

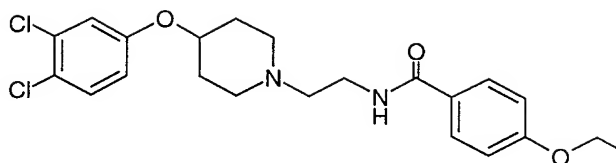
<sup>1</sup>H NMR: δ(DMSO) 8.22 (t, 1H), 7.8 (m, 2H), 7.49 (d, 1H), 7.25 (d, 1H), 7.00 (m, 3H), 4.7 (m, 1H), 4.45 (m, 1H), 3.36 (m, 2H), 2.73 (m, 2H), 2.48 (m, 2H), 2.29 (m, 2H), 1.91 (m, 2H), 1.60 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H)

Melting point: 113-15 °C

25 

### Example 4

#### N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-ethoxybenzamide



Prepared by the same method as Example 2 using 4-ethoxybenzoic acid without the addition of 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid (0.1g).

5

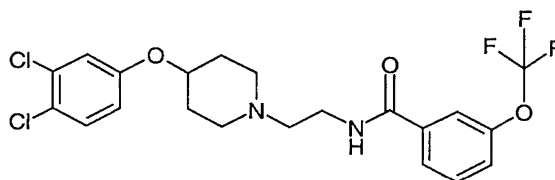
MS: ESI 437.14 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 8.22 (t, 1H), 7.79 (d, 2H), 7.49 (d, 1H), 7.25 (d, 1H), 7.00 (m, 3H), 4.5 (m, 1H), 4.07 (q, 2H), 3.37 (q, 2H), 2.73 (m, 2H), 2.47 (m, 2H), 2.30 (m, 2H), 1.91 (m, 2H), 1.60 (m, 2H), 1.34 (t, 3H)

10 Melting point: 118-20 °C

### Example 5

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide hydrochloride**



15

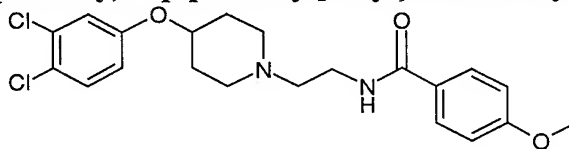
Prepared by the same method as Example 2 using 3-trifluoromethoxybenzoic acid to give the titled product as a solid (0.12g).

MS: ESI 477.09 (M+H)

20 <sup>1</sup>H NMR: δ(DMSO) 10.42 (bs, 1H), 9.11 (bm, 1H), 8.0 (d, 1H), 7.88 (s, 1H), 7.6 (m, 3H), 7.37 (m, 1H), 7.06 (m, 1H), 4.70 (m, 1H), 3.71 (m, 3H), 3.48 (d, 1H), 3.20 (m, 4H), 2.2 (m, 4H)

Melting point: 180-82 °C

25 **Example 6**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide**

Prepared by the same method as Example 2 using 4-methoxybenzoic without the addition of 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid (0.11g).

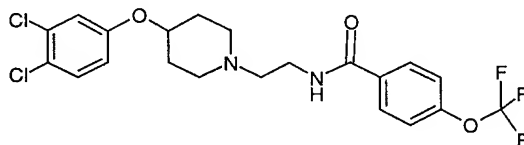
5

MS: ESI 423.12 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 8.42 (t, 1H), 7.81 (m, 2H), 7.49 (d, 1H), 7.25 (d, 1H), 6.98 (s, 3H), 4.4 (m, 1H), 3.8 (s, 3H), 3.35 (q, 2H), 2.73 (m, 2H), 2.47 (m, 2H), 2.30 (m, 2H), 1.91 (m, 2H), 1.60 (m, 2H)

10 

Melting point: 110-12 °C

**Example 7****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethoxy)benzamide hydrochloride**

15

Prepared by the same method as Example 2 using 4-trifluoromethoxybenzoic acid to give the titled product as a solid (0.19g).

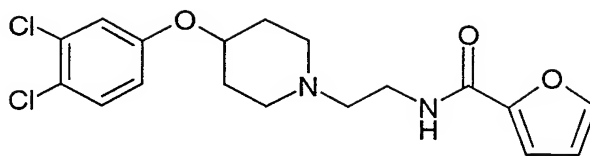
MS: ESI 477 (M+H)

20 

<sup>1</sup>H NMR: δ(DMSO) 10.5 (bs, 1H), 9.06 (m, 1H), 8.07 (dd, 2H), 7.55 (t, 1H), 7.49 (d, 2H), 7.36 (dd, 1H), 7.10-7.02 (m, 1H), 4.72 (m, 1H), 3.70 (m, 3H), 3.47 (d, 1H), 3.14 (m, 2H), 2.25 (m, 2H), 2.02 (m, 2H)

Melting point: 184-187 °C

25 **Example 8****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide hydrochloride**



Prepared by the same method as Example 2 using furan-2-carboxylic acid to give the titled product as a solid (0.14g).

5

MS: ESI 383.09 (M+H)

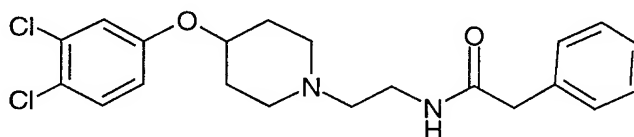
$^1\text{H}$  NMR:  $\delta$ (DMSO) 10.43 (bm, 1H), 8.76 (t, 1H), 7.87 (s, 1H), 7.55 (t, 1H), 7.36 (dd, 1H), 7.21 (d, 1H), 7.06 (m, 1H), 6.64 (dd, 1H), 4.83-4.61 (m, 1H), 3.65 (m, 3H), 3.45 (d, 1H), 3.08 (m, 4H), 2.1 (m, 4H)

10 

Melting point: 225-28 °C

### Example 9

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide hydrochloride**



15

Prepared by the same method as Example 2 using phenylacetic acid to give the titled product as a solid (0.12g).

MS: ESI 407 (M+H)

20 

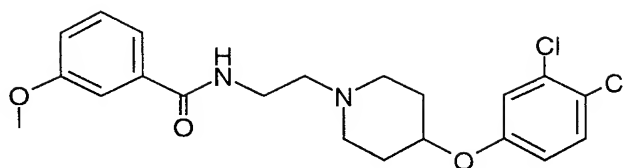
$^1\text{H}$  NMR:  $\delta$ (DMSO) 10.28 (bm, 1H), 8.46 (bm, 1H), 7.56 (t, 1H), 7.3 (m, 6H), 7.10 (m, 1H), 4.81/4.58 (m, 1H), 3.58 (d, 1H), 3.46 (m, 4H), 3.10 (m, 4H), 2.15 (m, 5H)

Melting point: 135-38 °C

### Example 10

25 

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride**



The product of Example 1 step (iv) (2.0g) was dissolved in dichloromethane (490ml), triethylamine (1.85ml) and 3-methoxybenzoyl chloride (0.66g) were added. After 72 hours at room temperature, water was added, the organic phase separated, dried and concentrated  
5 to a gum. The product was dissolved in dichloromethane and treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.88g).

MS: ESI 423.12 (M+H)

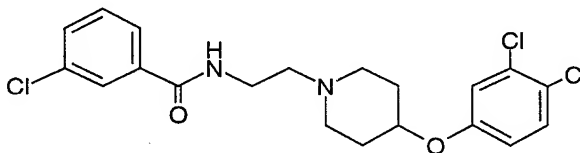
<sup>1</sup>H NMR:  $\delta$ (DMSO) 10.6-10.5 (m, 1H), 9.92 (s, 1H), 7.54 (m, 3H), 7.38 (m, 2H),  
10 7.08 (m, 2H), 4.84/4.62 (m 1H), 3.82 (s, 3H), 3.45 (m, 8H), 2.27 (m, 4H).

Melting point: 72-73 °C

### Example 11

#### 3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide

#### hydrochloride



The product of Example 1 step (iv) (0.15g) was dissolved in DMF (3ml), N,N-diisopropylethylamine (0.3ml) and 3-chlorobenzoyl chloride (0.054ml) were added. After 2 hours at room temperature, water and ethyl acetate were added, the organic phase separated  
20 dried and concentrated. The residue was purified by chromatography (dichloromethane : methanol, 95:5) to give an oil which was dissolved in ether and 1.0M ethereal hydrogen chloride solution added to give the titled product as a solid (0.12g).

MS: ESI 427.07 (M+H)



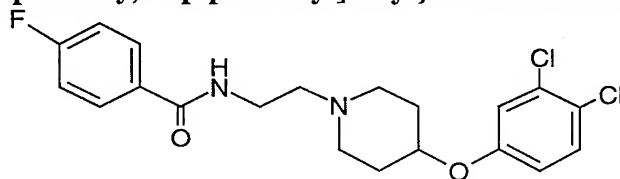
$^1\text{H}$  NMR:  $\delta$ (DMSO) 8.42 (t, 1H), 7.94-7.84 (m, 2H), 7.49 (d, 1H), 7.29 (m, 3H), 6.98 (dd, 1H), 4.44 (m, 1H), 3.36 (m, 2H), 2.74 (m, 2H), 2.48 (m, 2H), 2.29 (bt, 2H), 1.92 (m, 2H), 1.60 (m, 2H)

Melting point: 118 °C

5

### Example 12

#### N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide



Prepared by the same method as Example 11 using 4-fluorobenzoyl chloride without the addition of 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid (0.1g).

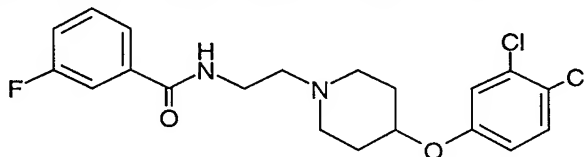
MS: ESI 411.10 (M+H)

$^1\text{H}$  NMR:  $\delta$ (DMSO) 10.46 (bs, 1H), 9.04 (s, 1H), 7.98 (s, 1H), 7.90 (d, 1H), 7.58 (m, 3H), 7.36 (dd, 1H), 7.05 (m, 1H), 4.84/4.60 (m, 1H), 3.69 (m, 3H), 3.48 (bd, 1H), 3.20 (m, 4H), 2.15 (m, 4H)

Melting point: 192 °C

### Example 13

#### N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide hydrochloride



Prepared by the same method as Example 11 using 3-fluorobenzoyl chloride to give the titled product as a solid (0.09g).

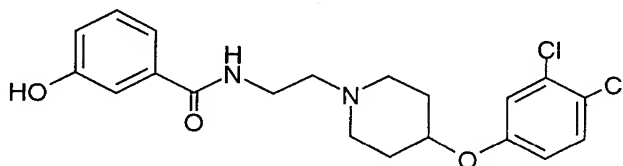
MS: ESI 411.10 (M+H)

25

$^1\text{H}$  NMR:  $\delta$ (DMSO) 10.67 (bs, 1H), 9.06 (s, 1H), 7.80 (m, 2H), 7.55 (m, 2H), 7.40 (m, 2H), 7.05 (m, 1H), 4.84/4.63(m, 1H), 3.70 (m, 3H), 3.28 (m, 3H), 2.20 (m, 4H)  
Melting point: 225 °C

5 **Example 14**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-hydroxybenzamide hydrochloride**



The product of Example 10 (0.15g) was dissolved in dichloromethane (10ml) and a  
10 solution of 1.0M  $\text{BBr}_3$  in dichloromethane (4ml) added. After 16 hours at room temperature the solvent was removed by evaporation, methanol was added and the solution concentrated. The residue was dissolved in 2M aqueous HCl solution, concentrated to dryness and the residue triturated under ether to give the titled product as a solid (0.1g).

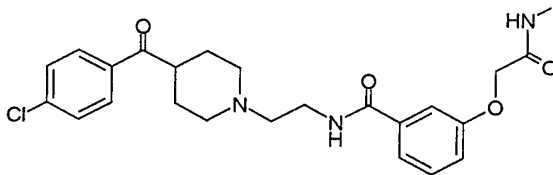
15 MS: ESI 409.10 (M+H)

$^1\text{H}$  NMR:  $\delta$ (DMSO) 9.98-9.4 (bs, 2H), 8.71 (t, 1H), 7.6 (dd, 1H), 7.4-7.2 (m, 4H), 7.05 (m, 1H), 6.95 (dd, 1H), 4.65 (m, 1H), 3.40 (m, 8H), 2.0 (m, 4H)

Melting point: 83-4 °C

20 **Example 15**

**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-[2-(methylamino)-2-oxoethoxy]benzamide hydrochloride**



25 (i) **[1-(2-Aminoethyl)-4-piperidinyl](4-chlorophenyl)methanone trifluoroacetate**

To a solution of (4-chlorophenyl)(4-piperidinyl)methanone hydrochloride (2.5g) and tert-butyl 2-bromoethylcarbamate (2.1g) in DMF was added triethylamine (2.9g), after 72 hours at room temperature water and ether were added. The organic phase was separated, dried and concentrated. The residue was dissolved in dichloromethane (40 ml), trifluoroacetic acid (10ml) added and the solution left for 20 hours. Evaporation of the solvent gave a sticky solid which was triturated under ether to give the sub-titled product as a solid (2.5g).

**(ii) N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride**

The product of step (i) (2.5g) was dissolved in dichloromethane (20ml), triethylamine (0.75ml) and 3-methoxybenzoyl chloride (0.276g) were added. After 16 hours, water was added, the organic phase separated, dried and concentrated to a gum. Purification by chromatography (ethyl acetate) gave a gum, which was treated with 1.0M ethereal hydrogen chloride solution to give the sub-titled product as a solid (0.3g).

MS: ESI 401.16 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 10.3 (bm, 1H), 8.95 (t, 1H), 8.0 (m, 2H), 7.6 (m, 2H), 7.5 (m, 2H), 7.4 (t, 1H), 7.05 (m, 1H), 3.8 (s, 3H), 3.68 (m, 4H), 3.28 (m, 5H), 2.0 (m, 4H).

Melting point: 196-7 °C

**(iii) N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-hydroxybenzamide hydrochloride**

Prepared by the method of Example 14 using the product of step (ii) above (0.24g) to give the sub-titled product as a solid (0.20g).

MS: ESI 387.14 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 8.62 (t, 1H), 8.05 (dd, 2H), 7.6 (dd, 2H), 7.25 (m, 3H), 6.95 (m, 1H), 4.26 (m, 9H), 2.0 (m, 4H)

Melting point: 90-91 °C

**(iv) N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-[2-(methylamino)-2-oxoethoxy]benzamide hydrochloride**

The product of step (iii) above (0.10g) was dissolved in DMF (3ml), Cs<sub>2</sub>CO<sub>2</sub> (0.23g) and 2-chloro-N-methylacetamide (0.26g) were added and the mixture heated at 80° C for 16 hours. The mixture was cooled to room temperature, water and ethyl acetate were added and the organic phase separated. Evaporation of the solvent gave a gum which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.05g).

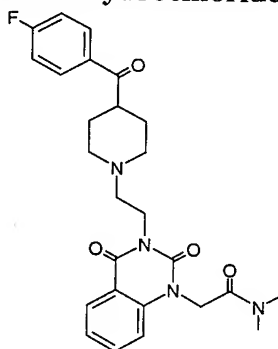
MS: ESI 458.18 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 10.6-10.2 (bm, 1H), 8.95 (bm, 1H), 8.1 (m, 2H), 7.55 (m, 8H), 7.14 (bd, 1H), 4.54 (s, 2H), 4.0 (m, 1H), 3.4 (m, 8H), 2.65 (d, 3H), 2.0 (m, 4H)

Melting point: 69-70 °C

**Example 16**

**2-[3-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl}-2,4-dioxo-3,4-dihydro-1(2H)-quinazolinyl]-N,N-dimethylacetamide hydrochloride**



3-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl}-2,4(1H,3H)-quinazolinedione was dissolved in DMF (5ml) and NaH ( 60% dispersion in mineral oil) added. After 0.5 hours, 2-chloro-N,N-dimethylacetamide was added and the solution stirred at room temperature for 16 hours. Water and ethyl acetate were added, the organic phase separated, dried and concentrated to an oil. Purification by chromatography (dichloromethane : methanol 95:5) gave an oil which was treated with 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid(0.015g).

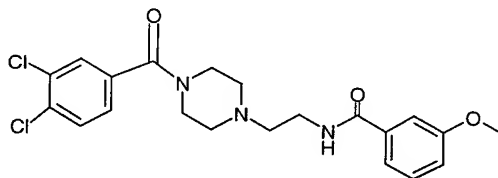
MS: ESI 481.22 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 8.08 (m, 3H), 7.76 (t, 1H), 7.40 (t, 2H), 7.32 (m, 2H), 5.05 (s, 2H), 4.36 (m, 1H), 3.76 (m, 3H), 3.39 (m, 2H), 3.15 (s, 3H), 2.87 (s, 3H), 2.02 (m, 2H), 1.81 (m, 2H), 1.28 (m, 2H)

Melting point: 245-246 °C

### Example 17

**N-{2-[4-(3,4-Dichlorobenzoyl)-1-piperazinyl]ethyl}-3-methoxybenzamide hydrochloride**



#### (i) **tert-Butyl 2-(1-piperazinyl)ethylcarbamate**

A mixture of benzaldehyde (21g) and 1-(2-aminoethyl)piperazine (25.8g) was stirred and heated under a Dean and Stark water separator for 20 hours. The cooled solution was treated portionwise with di-tert-butyl dicarbonate (48g), stirred for 72 hours and concentrated. The residue was treated with 1M aqueous KHSO<sub>4</sub> solution (220ml), stirred for 24 hours, ether was added and the organic phase separated. The aqueous phase was treated with 2M NaOH solution, dichloromethane was added and the organic phase separated. The combined organic phase was washed with brine, dried and concentrated to give the sub-titled product as an oil (30g).

MS: APCI(+ve) 230 (M+H)

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 3.43 (t, 4H), 2.8 (t, 2H), 2.45 (m, 6H), 1.5 (s, 9H).

#### (ii) **tert-Butyl 2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethylcarbamate**

The product from step (i) above (3g) was dissolved in pyridine (12ml), 3,4-dichlorobenzoyl chloride (2.05g) was added and the mixture stirred at room temperature for 18 hours. A

solid was collected by filtration and purified by chromatography (dichloromethane : methanol : 0.880 NH<sub>4</sub>OH, 90:9:1) to give the sub-titled product as an oil (3.59g).

MS: APCI(+ve ) 364( M+H)

5 <sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.33 (m, 3H), 7.04 (m, 1H), 6.76 (bs, 1H), 3.86 (s, 3H), 3.55 (q, 2H), 3.45 (t, 4H), 2.61 (t, 3H), 2.46 (t, 4H), 1.46 (s, 9H)

**(iii) [4-(2-Aminoethyl)-1-piperazinyl](3,4-dichlorophenyl)methanone trifluoroacetate**

The product from step (ii) above (3.3g) was dissolved in dichloromethane (50ml) and  
10 trifluoroacetic acid (10ml) added. After 16 hours at room temperature the solvent was removed to give the sub-titled product as an oil (5.9g).

MS: APCI(+ve ) 264( M+H)

15 **(iv) N-{2-[4-(3,4-Dichlorobenzoyl)-1-piperazinyl]ethyl}-3-methoxybenzamide hydrochloride**

The product from step (iii) above (0.15g) was dissolved in pyridine (2ml) and 3-methoxybenzoyl chloride (0.064g) added. After 16 hours at room temperature, water and ethyl acetate were added, the organic phase separated, dried and concentrated to an oil.  
20 Purification by chromatography (dichloromethane : methanol, 95:5) gave an oil which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.043g).

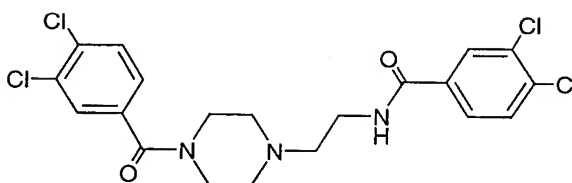
MS: ESI 436.12 (M+H)

25 <sup>1</sup>H NMR: δ(DMSO) 8.8 (bt, 1H), 7.34 (m, 2H), 7.43 (m, 4H), 7.14(m, 1H), 3.82(s, 3H), 3.48 (m,12H)

Melting point: 230 °C

**Example 18**

30 **3,4-Dichloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}benzamide**



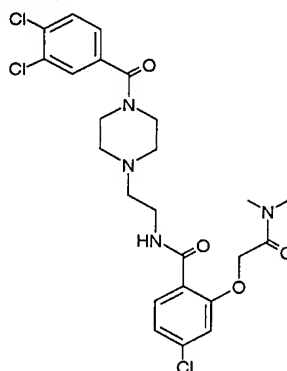
A solution of benzaldehyde (5.3g) and 1-(2-aminopiperazine) (6.45g) in toluene (100ml) was heated under a Dean and Stark water separator for 4 hours. The solution was cooled to room temperature and triethylamine (5.05g) added. A solution of 3,4-dichlorobenzoyl chloride (10.48g) in toluene (50ml) was added dropwise, the solution stirred at room temperature for 18 hours and water added. The organic phase was separated, dried and concentrated to a residue which was treated with 1N aqueous KHSO<sub>4</sub> solution (65ml). The mixture was stirred vigorously for 4 hours, ether was added, the aqueous phase separated and NaOH added. CHCl<sub>3</sub> was added, the organic phase separated, dried and concentrated to a gum. Purification by chromatography (dichloromethane : triethylamine, 95:5) gave the titled product as a foam (0.25g).

MS: ESI 474.03 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 8.8 (bt, 1H), 7.34 (m, 2H), 7.43 (m, 4H), 7.14 (m, 1H), 3.82 (s, 3H), 3.48 (m, 12H)

### Example 19

**4-Chloro-N-[2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl]-2-[2-(dimethylamino)-2-oxoethoxy]benzamide hydrochloride**



The product of Example 26 step (ii) (0.3g), 3,4-dichlorobenzoyl chloride (0.1g) and triethylamine (0.15g) were dissolved in dichloromethane (15ml). After 20 hours at room

temperature water was added, the organic phase separated, dried and evaporated to give a gum. Purification by chromatography (dichloromethane : methanol, 20:1) gave a solid which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.1g).

5

MS: ESI 541.11 (M+H)

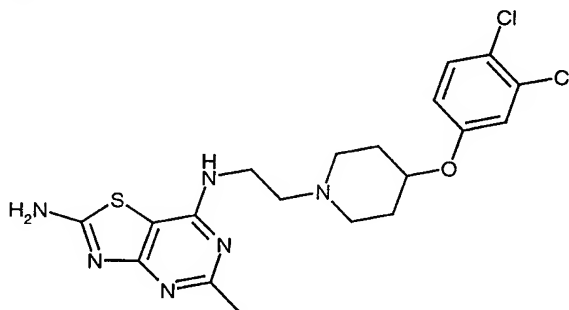
$^1\text{H}$  NMR  $\delta$ (DMSO-D<sub>6</sub>) 9.54 (t, 1H), 7.91 (d, 1H), 7.74 (m, 2H), 7.43 (m, 2H), 7.18 (d, 1H), 5.12 (s, 2H), 3.2-3.8 (m, 12H), 2.99 (s, 3H), 2.88 (s, 3H).

Melting point: 226-7 °C.

10

### Example 20

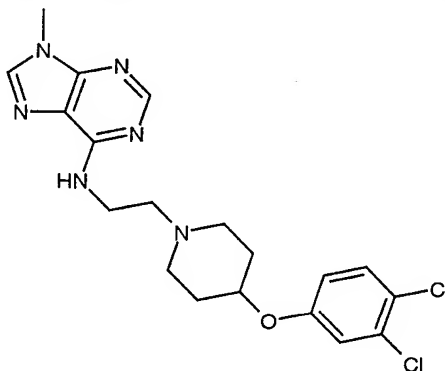
**N-7--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine**



15 MS: APCI(+ve) 453 (M+1)

### Example 21

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-9-methyl-9H-purin-6-amine**

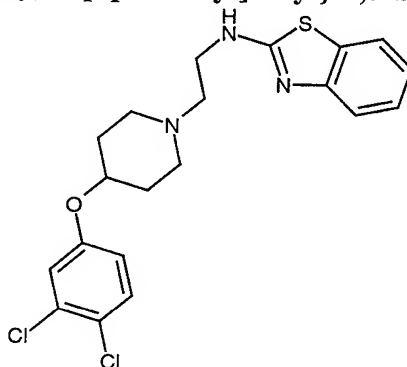




MS: APCI(+ve) 421 (M+1)

### Example 22

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzothiazol-2-amine**

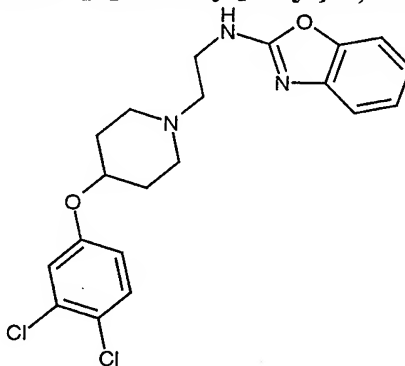


5

MS: APCI(+ve) 422 (M+1)

### Example 23

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzoxazol-2-amine**

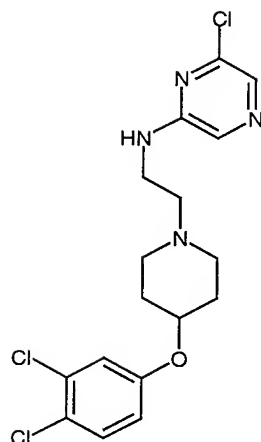


10

MS: APCI(+ve) 406 (M+1)

### Example 24

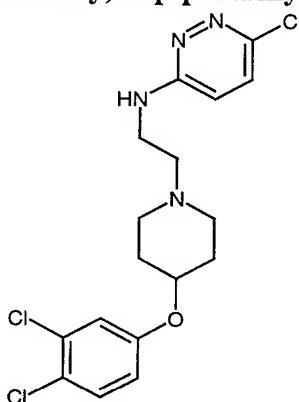
**6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrazinamine**



MS: APCI(+ve) 403 (M+1)

#### Example 25

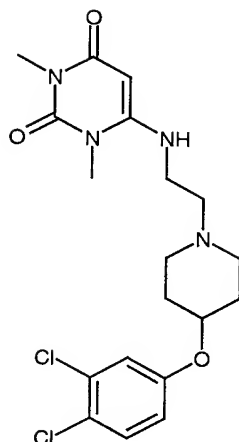
5 **6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-pyridazinamine**



MS: APCI(+ve) 403 (M+1)

#### Example 26

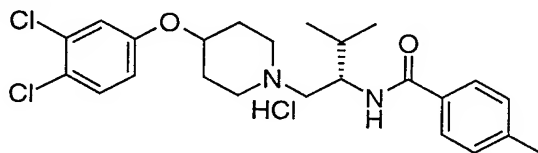
10 **6-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione**



MS: APCI(+ve) 427 (M+1)

### Example 27

5 **N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-4-methyl-benzamide, hydrochloride**



(i) **N-{1-[4-(3,4-Dichlorophenoxy)-piperidine-1-carbonyl]-2-methyl-propyl}-acetamide**

*N*-Boc Valine (1.13g) was dissolved in dichloromethane (5 ml) and EDC (0.99g) added,  
 10 after 5 min the product according to Example 1 step (ii) (1.44g) in dichloromethane (5 ml) was added in one portion. After 3 hours at room temperature, aqueous sodium bicarbonate solution and ethyl acetate were added. The organic phase was separated and the solvent removed to give the sub-titled compound as an oil (1.57 g) which was used in the next step without further purification.

15 (ii) **2-amino-1-[4-(3,4-dichlorophenoxy)-piperidine-1-yl]-3-methyl-butan-1-one**

The product of step (i) (1.57 g) was dissolved in dichloromethane (14 ml) and trifluoroacetic acid (4 ml) added. After 2 hours at room temperature the solvent was removed, ethyl acetate and 2N aqueous NaOH solution were added to give pH 8.0. The  
 20 organic phase was separated and concentrated to give the sub-titled product as an oil (1.24 g) which was used in the next step without further purification.

**(iii) 1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propylamine**

The product of step (ii) (1.12g) was dissolved in THF (10 ml) and Borane/THF complex (22.7 ml) added. The mixture was heated under reflux for 2 hours and cooled. The solvent was evaporated, the product dissolved in methanol (5ml) and 50% aqueous HCl solution added. The mixture was heated to 70 °C for 1 hour and cooled to room temperature. The solvent was removed, ethyl acetate and 2N aqueous NaOH solution were added to give pH 9.0. The organic phase was separated and the solvent evaporated to give the sub-titled compound as an oil (0.98 g) which used without further purification.

**(iv) N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-4-methyl-benzamide, hydrochloride**

The product of step (iii) (0.2g) was dissolved in dichloromethane (5ml), triethylamine (0.126 ml) and 4-methylbenzoyl chloride (0.097 ml) were added. After 2 hours at room temperature, ethyl acetate and aqueous NaHCO<sub>3</sub> solution were added, the organic phase separated and the solvent removed to leave an oil. Purification by reverse phase HPLC (with a gradient eluent system (25% MeCN/NH<sub>4</sub>OAc<sub>aq</sub> (0.1%) to 95% MeCN/NH<sub>4</sub>OAc<sub>aq</sub> (0.1%)) gave a gum. Addition of 1.0M ethereal hydrogen chloride solution gave the titled product as a solid (0.104 g).

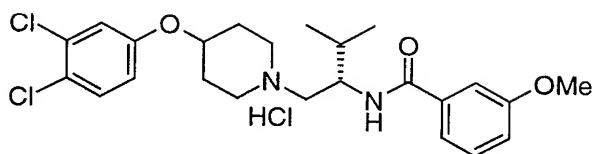
Melting point: 131-132°C

MS: ESI 450 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 8.45 (t, 1H), 7.00-7.90 (m, 7H), 4.79 (br s, 1H), 4.24-4.30 (m, 1H), 3.10-3.42 (m, 5H), 2.36 (s, 3H), 1.88-2.40 (m, 5H), 0.92 (t, 6H)

**Example 28**

**N-{1-[4-(3,4-Dichloro-phenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-methoxy-benzamide, hydrochloride**



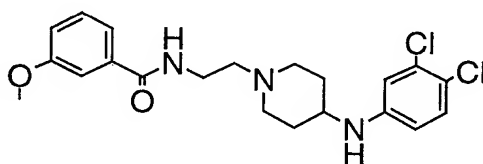
The product according to Example 27 step (iii) dissolved in dichloromethane (4 ml), triethylamine (0.090 ml) and 3-methoxybenzoyl chloride (0.077 ml) were added. After 2 hours at room temperature,  $\text{NaHCO}_3$  was added, the product extracted with ethyl acetate, the combined organic extracts dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Purification with reverse phase HPLC (with a gradient eluent system (25% MeCN/ $\text{NH}_4\text{OAc}_{\text{aq}}$  (0.1%) to 95% MeCN/ $\text{NH}_4\text{OAc}_{\text{aq}}$  (0.1%)) gave a gum. The product was dissolved in methanol and treated with 1.0M ethereal Hydrogen chloride solution to give the product as a solid (0.045 g).

MS: ESI 465 (M+H)

$^1\text{H}$  NMR:  $\delta$ (DMSO) 8.58-8.63 (m, 1H), 7.01-7.58 (m, 6H), 4.80 (br s, 1H), 4.23-4.59 (m, 1H), 3.83 (s, 3H), 3.04-3.60 (m, 4H), 1.89-2.14 (m, 5H), 0.85 (m, 6H)

### Example 29

**N-{2-[4-(3,4-Dichloroanilino)-1-piperidinyl]ethyl}-3-methoxybenzamide dihydrochloride**



#### (i) *tert*-Butyl 4-(3,4-dichloroanilino)-1-piperidinecarboxylate

A solution of 3,4-dichloroaniline (5g), *N*-*tert*-butoxycarbonyl-4-piperidone (11.7g), sodium triacetoxyborohydride (19.7g) and acetic acid (7ml) in dichloroethane (150ml) was stirred for 16 hours. 2M NaOH solution and ether were added, the organic phase separated, dried and concentrated. The residue was triturated under an isohexane : ethyl acetate, 4:1 mixture and the sub-titled product collected as a solid (7.25g).

MS: APCI(+ve) 345 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 7.23 (d, 1H), 6.77 (d, 1H), 6.57 (dd, 1H), 5.99 (d, 1H), 3.85 (bd, 2H), 3.40 (m, 1H), 2.90 (bm, 2H), 1.85 (m, 2H), 1.39 (s, 9H), 1.19 (m, 2H)

**(ii) N-(3,4-Dichlorophenyl)-4-piperidinamine trifluoroacetate**

5 The product of step (i) above (6.5g) was dissolved in dichloromethane (75ml) and trifluoroacetic acid (25ml) added. After 72 hours at room temperature the solution was evaporated and the residue triturated under ether to give the sub-titled product as a solid (6.3g).

10 MS: APCI(+ve) 245/7 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 8.65 (bs, 1H), 8.50 (bs, 1H), 7.26 (d, 1H), 6.81 (d, 1H), 6.60 (dd, 1H), 6.19 (bs, 1H), 3.53 (bs, 1H), 3.30 (m, 2H), 3.0 (m, 2H), 2.02 (m, 2H), 1.50 (m, 2H)

15 **(iii) tert-Butyl 2-[4-(3,4-dichloroanilino)-1-piperidinyl]ethylcarbamate**

The product from step (ii) above (2.0g), N-tert-butoxycarbonyl-2-bromoethanamine (1.0g) and N,N-di-isopropylethylamine (3.7ml) were dissolved in DMF (25ml) and stirred for 16 hours. Water and ethyl acetate were added, the organic phase separated, dried and evaporated to give a gum. Purification by chromatography (dichloromethane : methanol, 20 95:5) gave the sub-titled product as a solid (1.25g).

MS: APCI(+ve) 388/90 (M+H)

<sup>1</sup>H NMR: δ(DMSO) 7.22 (d, 1H), 6.73 (d, 1H), 6.62 (t, 1H), 6.54 (dd, 1H), 5.94 (d, 1H), 3.17 (m, 1H), 3.02 (m, 2H), 2.77 (bd, 2H), 2.31 (t, 3H), 2.06 (t, 2H), 1.84 (bd, 2H), 25 1.35 (m, 11H)

**(iv) 1-(2-Aminoethyl)-N-(3,4-dichlorophenyl)-4-piperidinamine trifluoroacetate**

The product from step (iii) above (1.2g) was dissolved in dichloromethane (30ml) and trifluoroacetic acid (10ml) added. After 72 hours at room temperature the reaction mixture

was evaporated and residue triturated under ether to give the sub-titled product as a solid (1.6g).

MS: APCI(+ve) 288/90 (M+H)

5

**(v) N-{2-[4-(3,4-Dichloroanilino)-1-piperidinyl]ethyl}-3-methoxybenzamide dihydrochloride**

The product of step (iv) above (0.5g) and triethylamine (1.1ml) were dissolved in DMF (10ml), 3-methoxybenzoylchloride (0.11ml) was added dropwise. After 2 hours, water and ethyl acetate were added, the organic phase separated, dried and evaporated. Purification of the residue by chromatography (dichloromethane : methanol, 95:5) gave an oil which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.15g).

MS: ESI 422.14 (M+H)

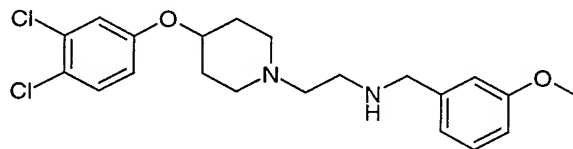
<sup>1</sup>H NMR:  $\delta$ (DMSO) 10.44 (bs, 1H), 8.93 (t, 1H), 7.51 (m, 2H), 7.40 (t, 1H), 7.26 (d, 1H), 7.11 (dd, 1H), 6.81 (d, 1H), 6.60 (dd, 1H), 3.82 (s, 3H), 2.68 (m, 4H), 3.25 (m, 5H), 2.09 (bd, 2H), 1.76 (m, 2H)

Melting point: 170 °C

20

**Example 30**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-(3-methoxybenzyl)amine dihydrochloride**



A suspension of the product of Example 1 step (iv) (0.11g) in a mixture of DMF (1.5ml) and 1,2-dichloroethane (3ml) was stirred under an atmosphere of nitrogen. Sodium triacetoxyborohydride (0.097g), 3-methoxybenzaldehyde (0.041g) and triethylamine (0.046g) were added and the mixture stirred for 18 hours at room temperature. Chloroform

and aqueous NaHCO<sub>3</sub> solution were added, the organic phase separated, dried and concentrated to a gum. Purification by chromatography (chloroform : triethylamine : methanol, 89 :10:1) gave an oil which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.067g).

5

MS: ESI 409.14 (M+H)

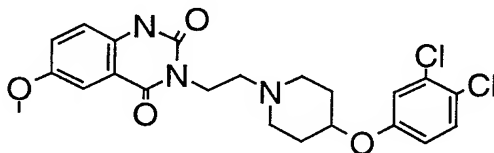
<sup>1</sup>H NMR: δ(DMSO) 7.50 (d, 1H), 7.30 (m, 3H), 7.12 (d, 1H), 7.03 (dd, 1H), 6.97 (dd, 1H), 4.71 (bm, 1H), 4.18 (s, 2H), 3.80 (s, 3H), 3.45 (bm, 4H), 2.23 (m, 6H), 2.04 (m, 2H),

Melting point: 247-51 °C

10

### Example 31

**3-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methoxy-2,4(1H,3H)-quinazolinedione**



15 (i) **2-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxybenzamide**

Prepared by the method of Example 2 using the product from Example 1 step (iv) (1.0g) and 2-amino-5-methoxybenzoic acid (0.418g) without the addition of 1.0M ethereal hydrogen chloride solution to give an oil which was purified by chromatography (dichloromethane : methanol, 95:5) to give the sub-titled product as an oil (0.82g).

20

MS: APCI(+ve) 438 (M+H)

(ii) **3-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methoxy-2,4(1H,3H)-quinazolinedione**

25

The product of step (i) above was dissolved in toluene (10ml). A solution of phosgene 2.0M in toluene (10ml) was added, the solution heated under reflux for 1 hour and cooled. Ethyl acetate and aqueous NaHCO<sub>3</sub> solution were added, the organic phase separated,



dried and concentrated to leave a residue which was purified by chromatography (dichloromethane : methanol, 95:5). The titled product was obtained as a solid (0.11g).

MS: ESI 464.11 (M+H)

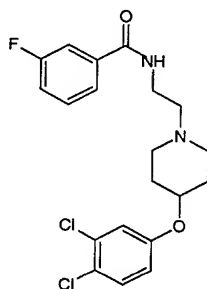
5  $^1\text{H}$  NMR:  $\delta$ (DMSO) 7.49 (dd, 1H), 7.36 (d, 1H), 7.30 (dd, 1H), 7.24 (d, 1H), 6.98 (dd, 1H), 4.44 (m, 1H), 4.03 (t, 3H), 3.80 (s, 3H), 2.76 (m, 2H), 2.32 (m, 2H), 1.89 (m, 2H), 1.57 (m, 2H)

Melting point: 190 °C

10 The compounds of following Examples 32 to 125 were prepared by methods analogous to the method of Example 10.

### Example 32

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide**

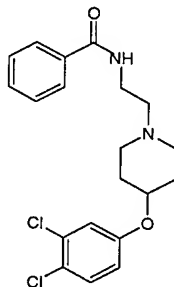


15

MS: APC1 (+ve) BP 411

### Example 33

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

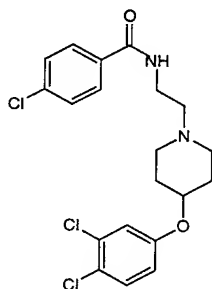


20

MS: APC1 (+ve) BP 393

### Example 34

**4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

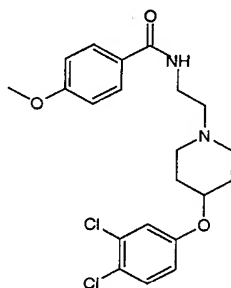


5

MS: APC1 (+ve) BP 429

### Example 35

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide**



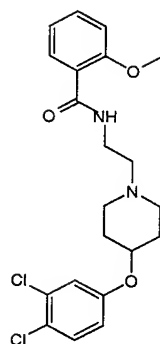
10

MS: APC1 (+ve) BP 423

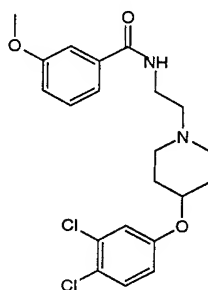
### Example 36

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxybenzamide**

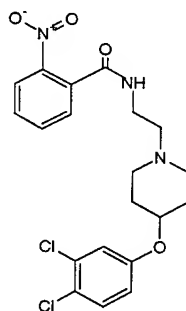
53



MS: APC1 (+ve) BP 423

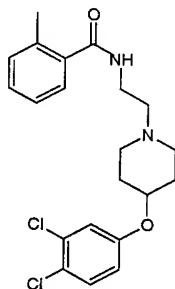
**Example 37**5 **N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide**

MS: APC1 (+ve) BP 423

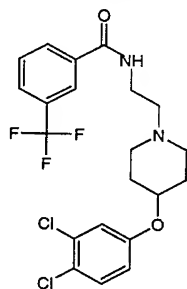
**Example 38**10 **N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-nitrobenzamide**

MS: APC1 (+ve) BP 438

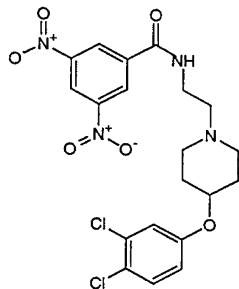
**Example 39**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methylbenzamide**

MS: APC1 (+ve) BP 407

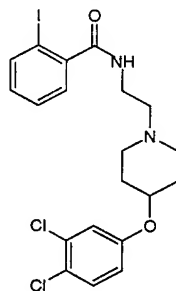
**5 Example 40****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide**

MS: APC1 (+ve) BP 461

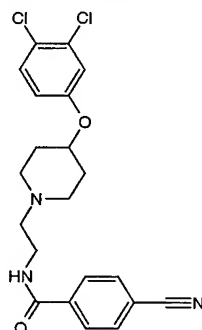
**10 Example 41****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-dinitrobenzamide**

MS: APC1 (+ve) BP 483

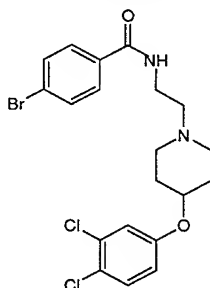
**15 Example 42**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-iodobenzamide**

MS: APC1 (+ve) BP 519

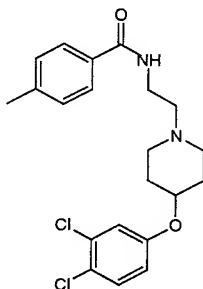
5 **Example 43****4-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 418

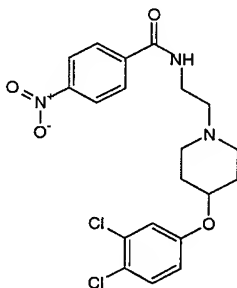
10 **Example 44****4-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 473

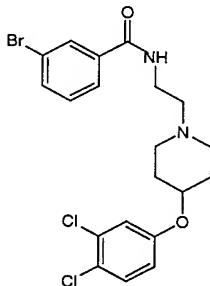
15 **Example 45**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methylbenzamide**

MS: APC1 (+ve) BP 407

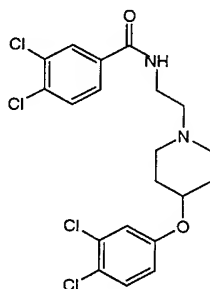
**5 Example 46****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-nitrobenzamide**

MS: APC1 (+ve) BP 438

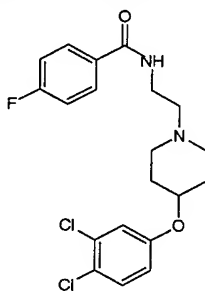
**10 Example 47****3-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 473

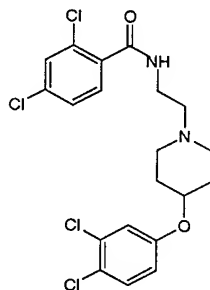
**15 Example 48**

**3,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 463

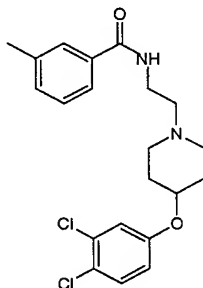
**5 Example 49****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide**

MS: APC1 (+ve) BP 411

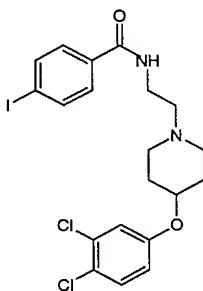
**10 Example 50****2,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 463

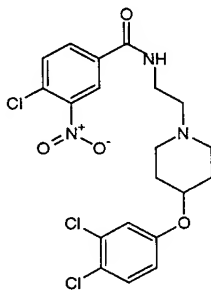
**15 Example 51**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methylbenzamide**

MS: APC1 (+ve) BP 407

**5 Example 52****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-iodobenzamide**

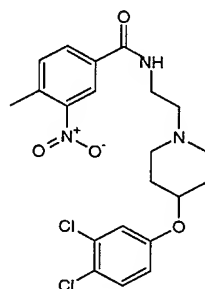
MS: APC1 (+ve) BP 519

**10 Example 53****4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-nitrobenzamide**

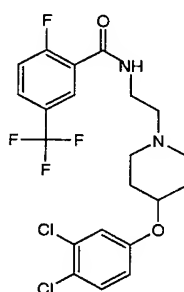
MS: APC1 (+ve) BP 472

**15 Example 54**



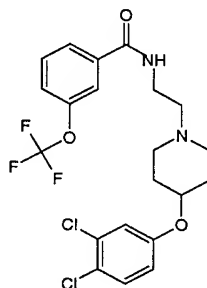
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide**

MS: APC1 (+ve) BP 452

**Example 55****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-5-(trifluoromethyl)benzamide**

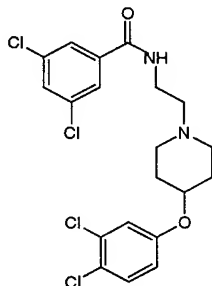
MS: APC1 (+ve) BP 479

10

**Example 56****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide**

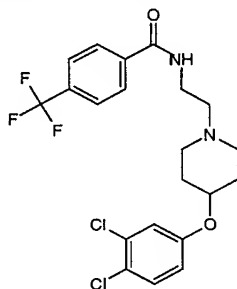
MS: APC1 (+ve) BP 477

15

**Example 57****3,5-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

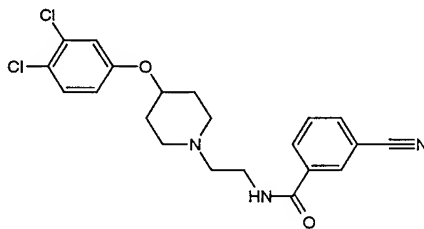
MS: APC1 (+ve) BP 463

5

**Example 58****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)benzamide**

MS: APC1 (+ve) BP 461

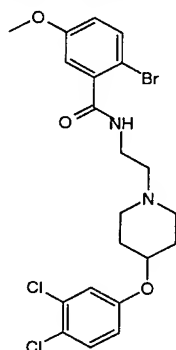
10

**Example 59****3-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

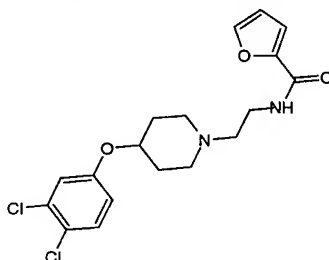
MS: APC1 (+ve) BP 418

15

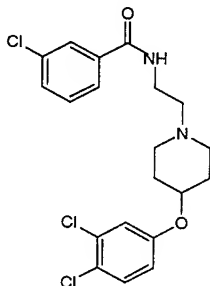
**Example 60**

**2-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxybenzamide**

MS: APC1 (+ve) BP 503

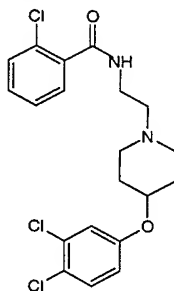
**Example 61****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide**

MS: APC1 (+ve) BP 383

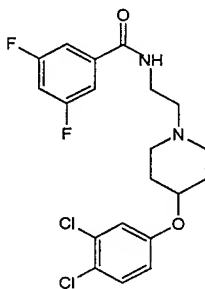
**Example 62****3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 427

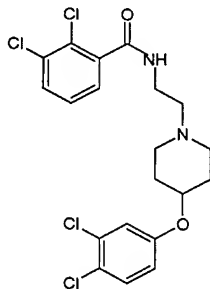
**Example 63**

**2-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 429

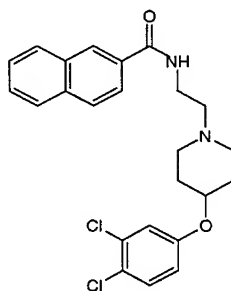
**Example 64****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-difluorobenzamide**

MS: APC1 (+ve) BP 429

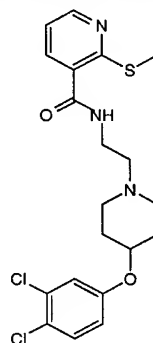
**Example 65****2,3-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 463

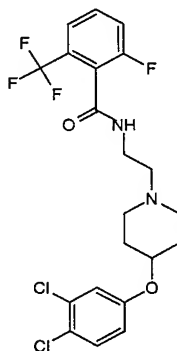
**Example 66**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-naphthamide**

MS: APC1 (+ve) BP 442

**5 Example 67****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide**

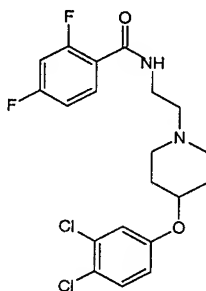
MS: APC1 (+ve) BP 440

**10 Example 68****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-6-(trifluoromethyl)benzamide**

MS: APC1 (+ve) BP 479

### Example 69

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-difluorobenzamide**

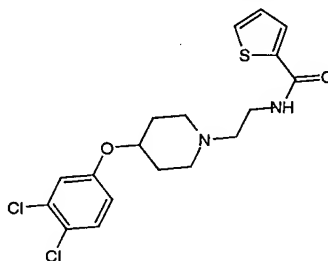


5

MS: APC1 (+ve) BP 429

### Example 70

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-thiophenecarboxamide**

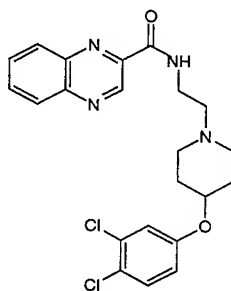


10

MS: APC1 (+ve) BP 399

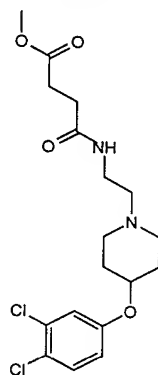
### Example 71

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide**

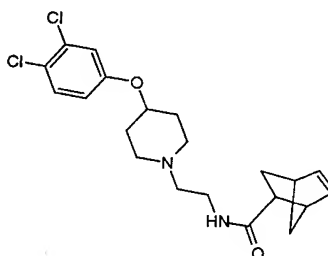


15

MS: APC1 (+ve) BP 445

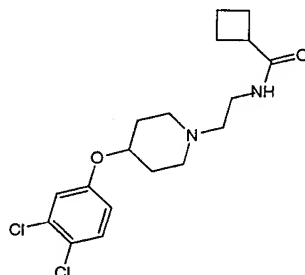
**Example 72****Methyl 4-({2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}amino)-4-oxobutanoate**

5 MS: APC1 (+ve) BP 403

**Example 73****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide**

10

MS: APC1 (+ve) BP 409

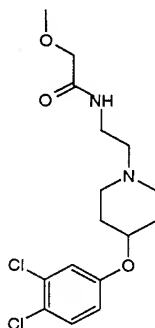
**Example 74****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclobutanecarboxamide**

15

MS: APC1 (+ve) BP 371

**Example 75**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxyacetamide**

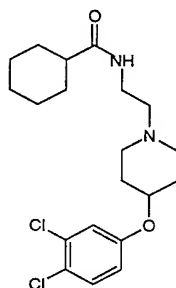


5

MS: APC1 (+ve) BP 361

**Example 76**

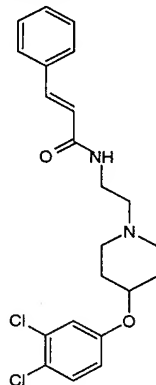
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclohexanecarboxamide**



10

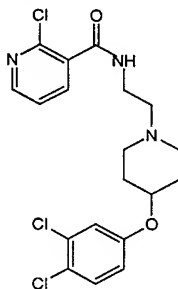
MS: APC1 (+ve) BP 399



**Example 77****(E)-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide**

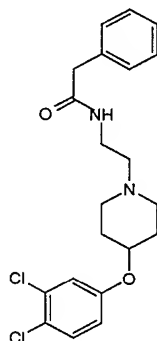
MS: APC1 (+ve) BP 419

5

**Example 78****2-Chloro-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}nicotinamide**

MS: APC1 (+ve) BP 430

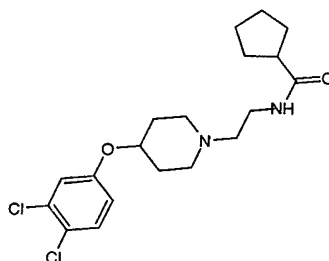
10

**Example 79****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide**

MS: APC1 (+ve) BP 407

### Example 80

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclopentanecarboxamide**

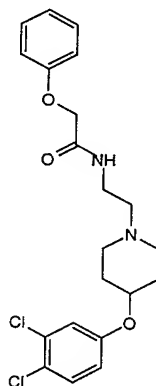


5

MS: APC1 (+ve) BP 385

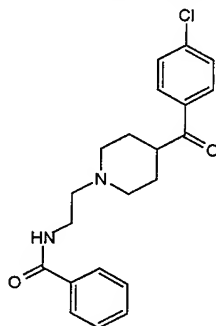
### Example 81

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenoxyacetamide**



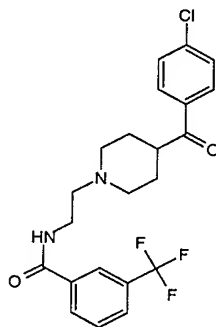
10

MS: APC1 (+ve) BP 423

**Example 82****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}benzamide**

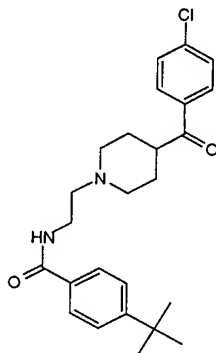
MS: APC1 (+ve) BP 371

5

**Example 83****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide**

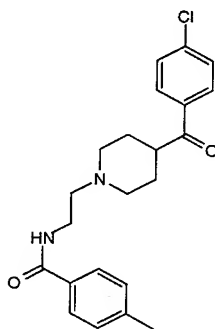
MS: APC1 (+ve) BP 439

10

**Example 84****4-(tert-Butyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 427

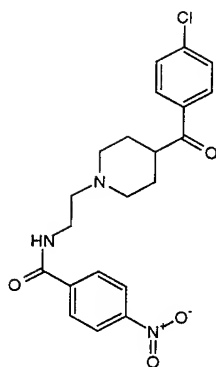
5

**Example 85****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methylbenzamide**

MS: APC1 (+ve) BP 385

10

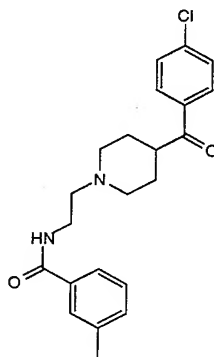
**Example 86****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-nitrobenzamide**



MS: APC1 (+ve) BP 416

#### Example 87

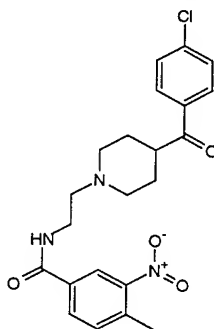
5 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-methylbenzamide



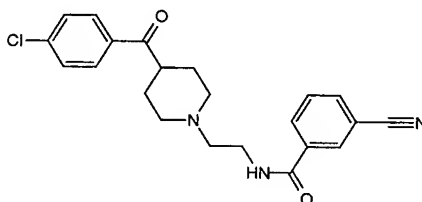
MS: APC1 (+ve) BP 385

#### Example 88

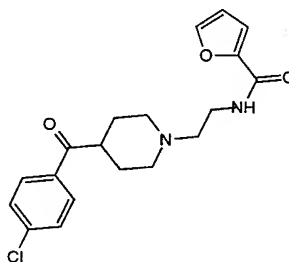
10 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide



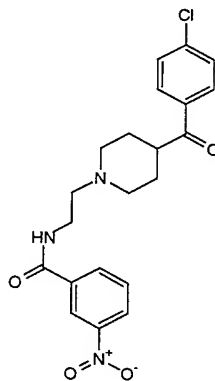
MS: APC1 (+ve) BP 430

**Example 89****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-cyanobenzamide**

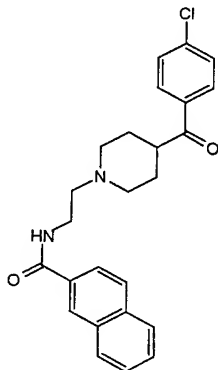
5 MS: APC1 (+ve) BP 396

**Example 90****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-furamide**

10 MS: APC1 (+ve) BP 361

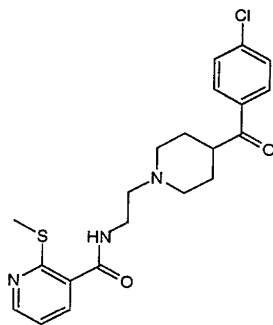
**Example 91****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-nitrobenzamide**

15 MS: APC1 (+ve) BP 416

**Example 92****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-naphthamide**

MS: APC1 (+ve) BP 421

5

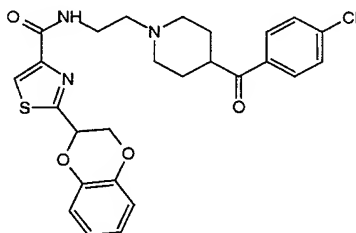
**Example 93****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide**

MS: APC1 (+ve) BP 418

10

**Example 94**

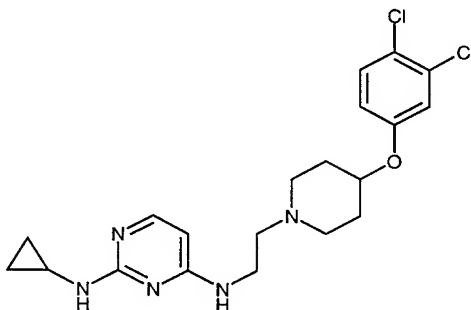
**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(2,3-dihydro-1,4-benzodioxin-2-yl)-1,3-thiazole-4-carboxamide**



5 MS: APC1 (+ve) BP 512

**Example 95**

**N-2-Cyclopropyl-N-4-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine**



10

MS: APCI(+ve) 422 (M+1)

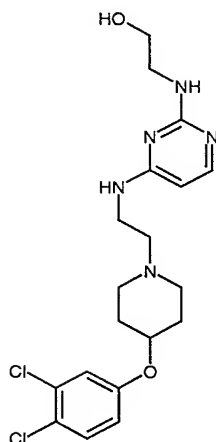
**Example 96**

**2-{[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-pyrimidinyl]amino}-1-ethanol**

15



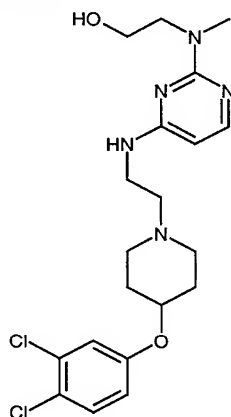
75



MS: APCI(+ve) 426 (M+1)

### Example 97

5    **2-[[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidiny]ethyl}amino)-2-pyrimidinyl](methylamino)-1-ethanol**

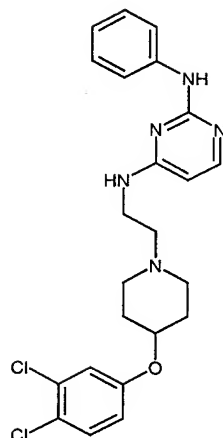


MS: APCI(+ve) 440 (M+1)

### 10    Example 98

**N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidiny]ethyl}-N~2~-phenyl-2,4-pyrimidinediamine**

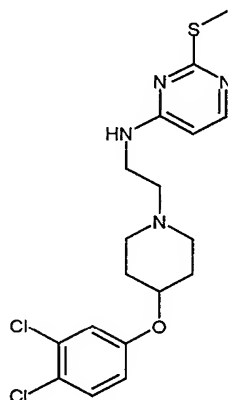
76



MS: APCI(+ve) 458 (M+1)

### Example 99

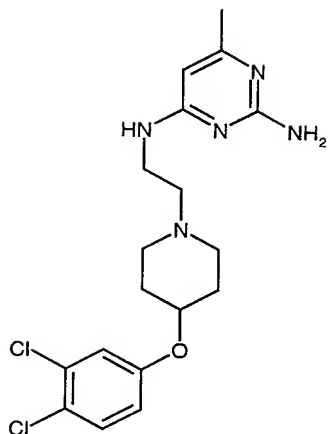
5 **N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfonyl)-4-pyrimidinamine**



MS: APCI(+ve) 413 (M+1)

### 10 Example 100

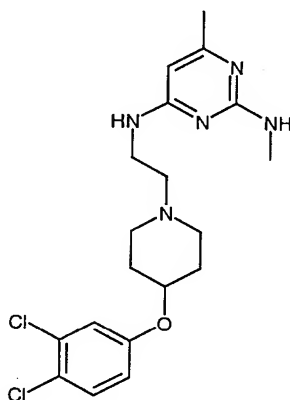
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfonyl)-4-pyrimidinamine**



MS: APCI(+ve) 396 (M+1)

### Example 101

5 **N-(2-((3,4-Dichlorophenoxy)methyl)piperidin-1-yl)-N-(2,6-dimethyl-2,4-pyrimidinediamine)**

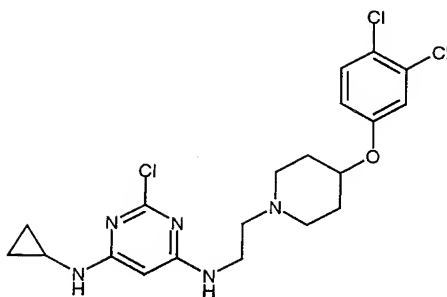


MS: APCI(+ve) 410 (M+1)

### 10 Example 102

**2-Chloro-N-(cyclopropyl)-N-(2-((3,4-dichlorophenoxy)methyl)piperidin-1-yl)-4,6-pyrimidinediamine**

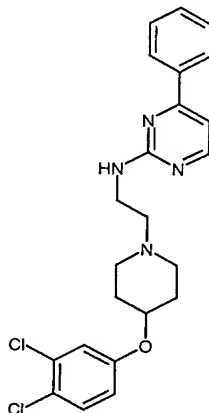
78



MS: APCI(+ve) 456 (M+1)

### Example 103

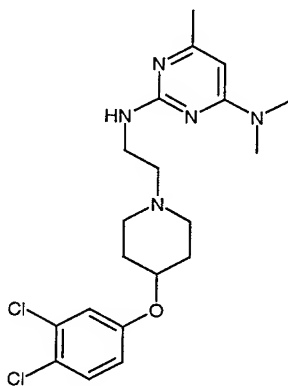
5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenyl-2-pyrimidinamine



MS: APCI(+ve) 443 (M+1)

### Example 104

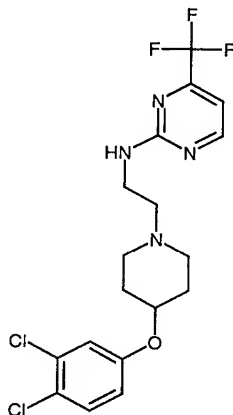
10 N~2~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine



MS: APCI(+ve) 424 (M+1)

### Example 105

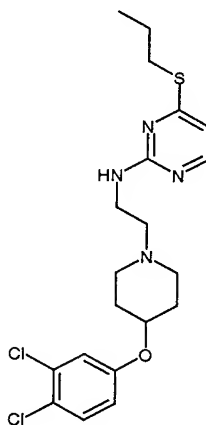
5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)-2-pyrimidinamine



MS: APCI(+ve) 435 (M+1)

### Example 106

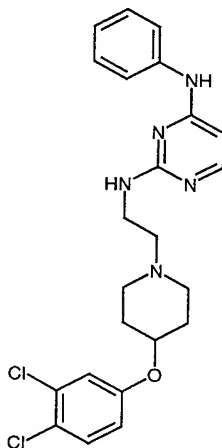
10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(propylsulfanyl)-2-pyrimidinamine



MS: APCI(+ve) 441 (M+1)

**Example 107**

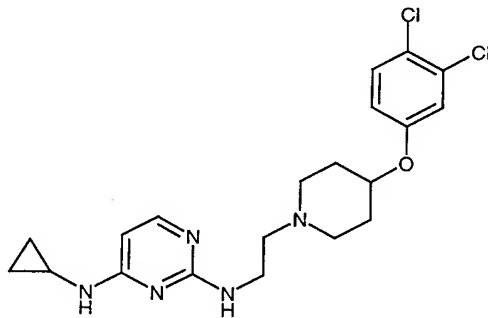
**N~2~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~-phenyl-2,4-pyrimidinediamine**



5 MS: APCI(+ve) 458 (M+1)

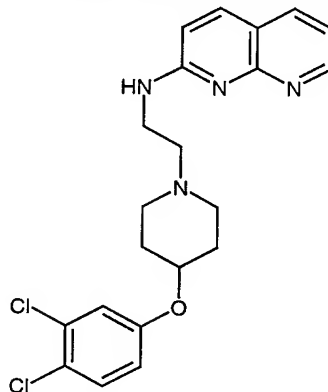
**Example 108**

**N~4~-Cyclopropyl-N~2~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine**



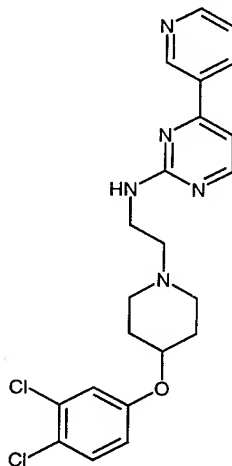
10

MS: APCI(+ve) 422 (M+1)

**Example 109****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}[1,8]naphthyridin-2-amine**

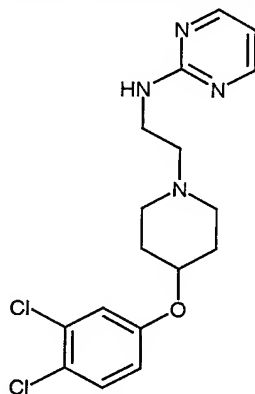
MS: APCI(+ve) 417 (M+1)

5

**Example 110****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-pyridinyl)-2-pyrimidinamine**

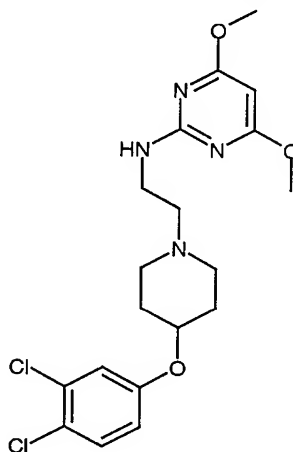
MS: APCI(+ve) 444 (M+1)

10

**Example 111****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrimidinamine**

MS: APCI(+ve) 367 (M+1)

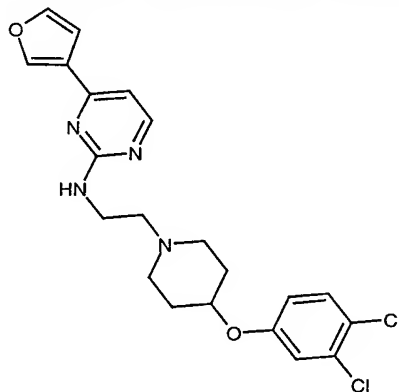
5

**Example 112****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-dimethoxy-2-pyrimidinamine**

MS: APCI(+ve) 427 (M+1)

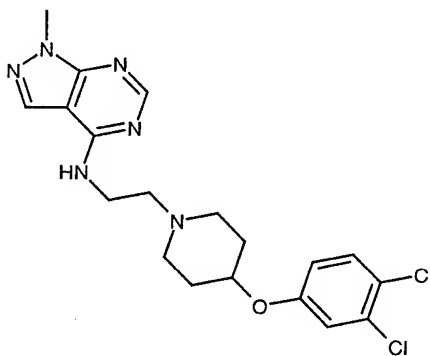
10



**Example 113****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-furyl)-2-pyrimidinamine**

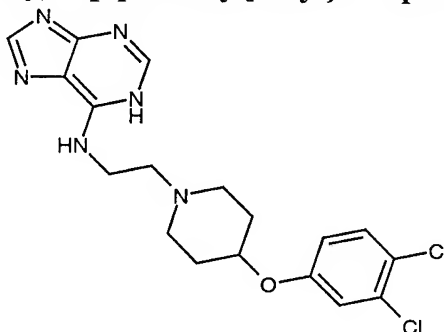
MS: APCI(+ve) 433 (M+1)

5

**Example 114****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine**

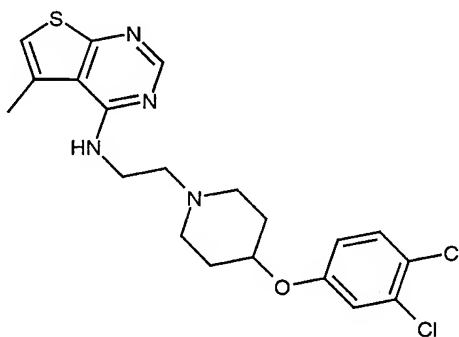
10

MS: APCI(+ve) 421 (M+1)

**Example 115****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-purin-6-amine**

MS: APCI(+ve) 407 (M+1)

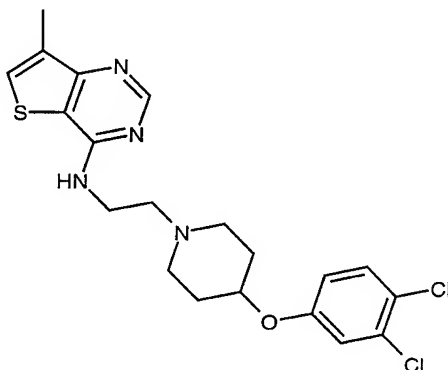
5

**Example 116****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methylthieno[2,3-d]pyrimidin-4-amine**

10 MS: APCI(+ve) 437 (M+1)

**Example 117**

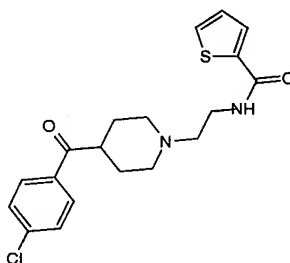
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methylthieno[3,2-d]pyrimidin-4-amine**



5 MS: APCI(+ve) 437 (M+1)

**Example 118**

**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-thiophenecarboxamide**

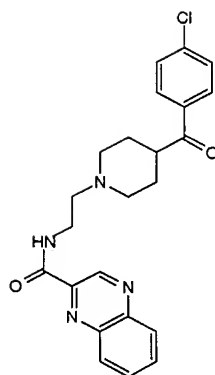


10 MS: APCI (+ve) BP 377

**Example 119**

**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide**

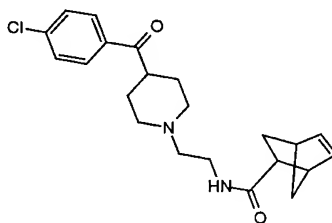
86



MS: APC1 (+ve) BP 423

**Example 120**

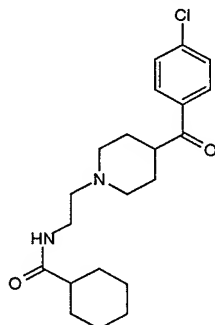
5 **N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide**



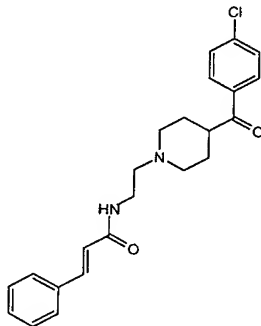
MS: APC1 (+ve) BP 387

10 **Example 121**

**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}cyclohexanecarboxamide**

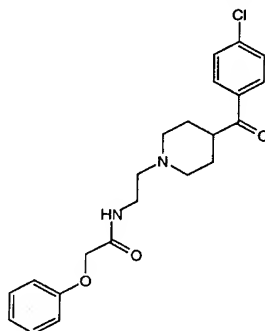


MS: APC1 (+ve) BP 377

**Example 122****(E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide**

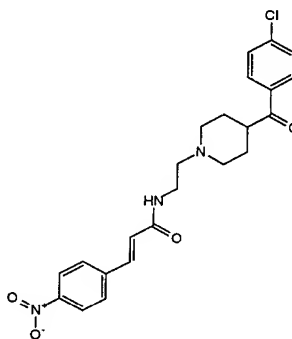
MS: APC1 (+ve) BP 397

5

**Example 123****N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-phenoxyacetamide**

MS: APC1 (+ve) BP 401

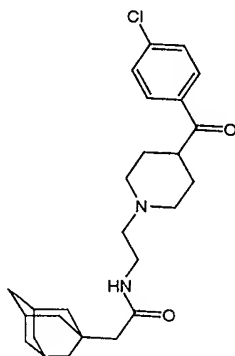
10

**Example 124****(E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(4-nitrophenyl)-2-propenamide**

MS: APC1 (+ve) BP 442

### Example 125

2-(1-Adamantyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}acetamide



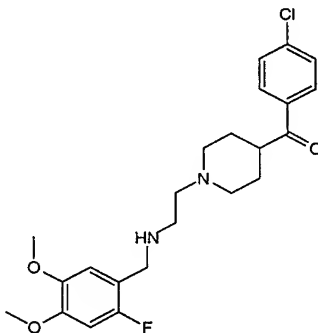
5

MS: APC1 (+ve) BP 443

The compounds of following Examples 126 to 168 were prepared by methods analogous to  
10 the method of Example 30.

### Example 126

(4-Chlorophenyl)(1-{2-[(2-fluoro-4,5-dimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone

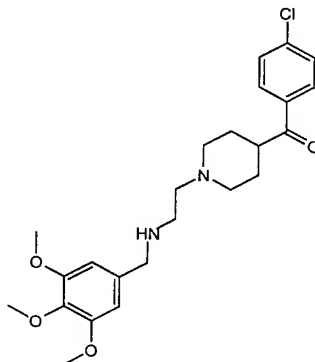


15

MS: APC1 (+ve) BP 435

### Example 127

**(4-Chlorophenyl)(1-{2-[(3,4,5-trimethoxybenzyl)amino]ethyl}-4-piperidinyloxy)methanone**

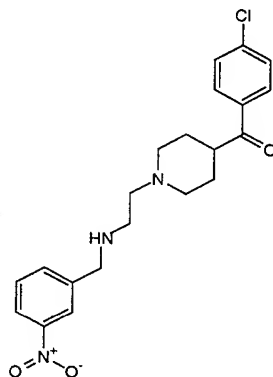


MS: APC1 (+ve) BP 447

5

**Example 128**

**(4-Chlorophenyl)(1-{2-[(3-nitrobenzyl)amino]ethyl}-4-piperidinyloxy)methanone**

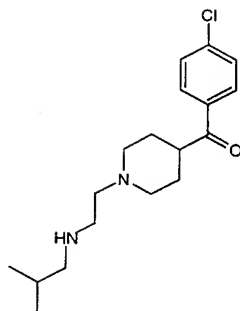


MS: APC1 (+ve) BP 402

10

**Example 129**

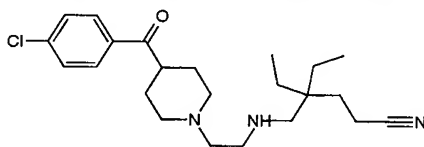
**(4-Chlorophenyl){1-[2-(isobutylamino)ethyl]-4-piperidinyloxy)methanone**



MS: APC1 (+ve) BP 323

### Example 130

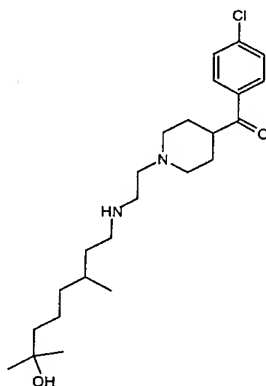
5 **4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4-ethylhexanenitrile**



MS: APC1 (+ve) BP 404

### Example 131

10 **(4-Chlorophenyl)(1-{2-[(7-hydroxy-3,7-dimethyloctyl)amino]ethyl}-4-piperidinyl)methanone**

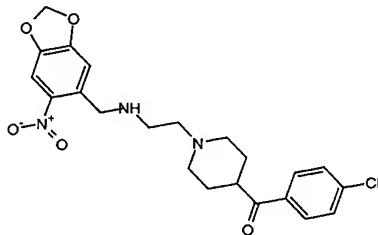


MS: APC1 (+ve) BP 423

15 **Example 132**



**(4-Chlorophenyl)[1-(2-[[6-nitro-1,3-benzodioxol-5-yl)methyl]amino}ethyl)-4-piperidinyl]methanone**

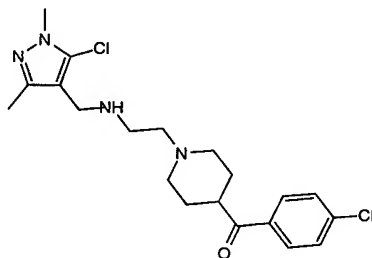


MS: APC1 (+ve) BP 446

5

### Example 133

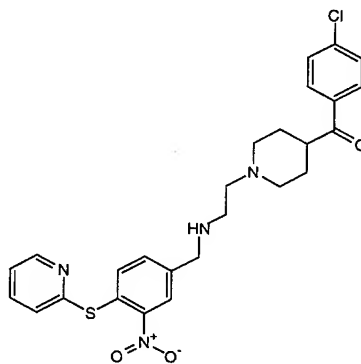
**[1-(2-[[5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone**



10 MS: APC1 (+ve) BP 409

### Example 134

**(4-Chlorophenyl)[1-(2-{[3-nitro-4-(2-pyridinylsulfanyl)benzyl]amino}ethyl)-4-piperidinyl]methanone**

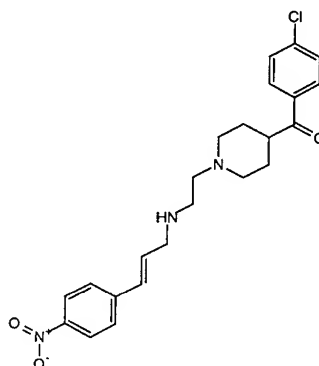


15

MS: APC1 (+ve) BP 511

**Example 135**

**(4-Chlorophenyl)[1-(2-{[(E)-3-(4-nitrophenyl)-2-propenyl]amino}ethyl)-4-piperidiny]methanone**



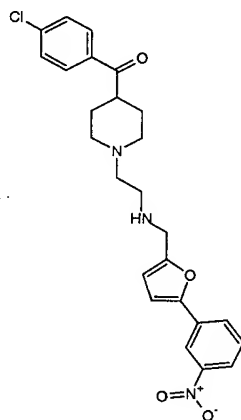
5

MS: APC1 (+ve) BP 428

**Example 136**

**(4-Chlorophenyl){1-[2-({[5-(3-nitrophenyl)-2-furyl]methyl}amino)ethyl]-4-piperidiny]methanone**

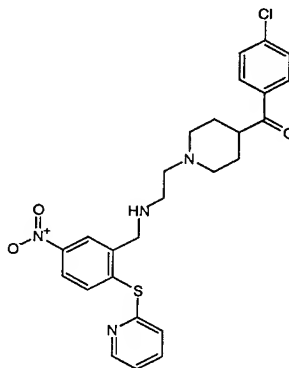
10



MS: APC1 (+ve) BP 468

**Example 137**

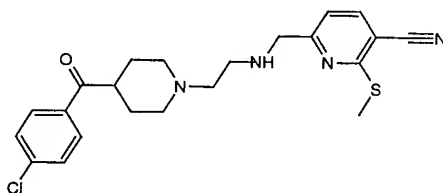
**(4-Chlorophenyl)[1-(2-{[5-nitro-2-(2-pyridinylsulfanyl)benzyl]amino}ethyl)-4-piperidinyl]methanone**



5 MS: APC1 (+ve) BP 511

**Example 138**

**6-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-2-(methylsulfanyl)nicotinonitrile**

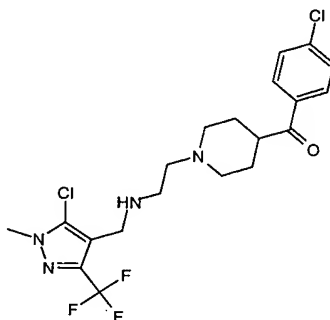


10

MS: APC1 (+ve) BP 429

**Example 139**

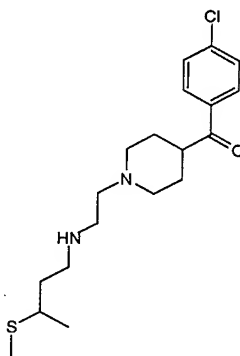
**{1-[2-({[5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}amino)ethyl]-4-piperidiny](4-chlorophenyl)methanone**



5 MS: APC1 (+ve) BP 463

**Example 140**

**(4-Chlorophenyl)[1-(2-{[3-(methylsulfanyl)butyl]amino}ethyl)-4-piperidiny]methanone**

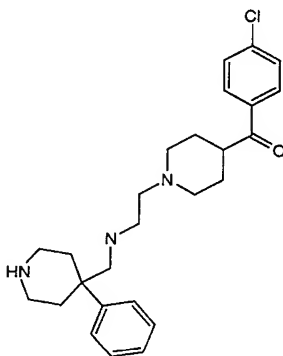


10

MS: APC1 (+ve) BP 369

**Example 141**

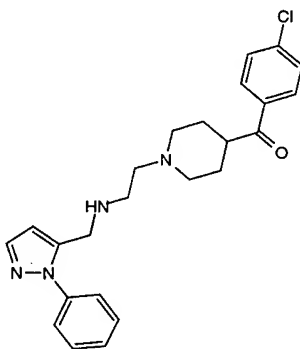
**(4-Chlorophenyl)[1-(2-[[4-(4-phenyl-4-piperidinyl)methyl]amino}ethyl)-4-piperidinyl]methanone**



5 MS: APC1 (+ve) BP 440

**Example 142**

**(4-Chlorophenyl)[1-(2-[[1-(1-phenyl-1H-pyrazol-5-yl)methyl]amino}ethyl)-4-piperidinyl]methanone**

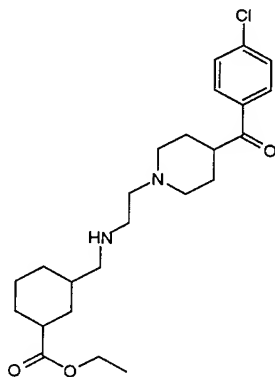


10

MS: APC1 (+ve) BP 423

**Example 143**

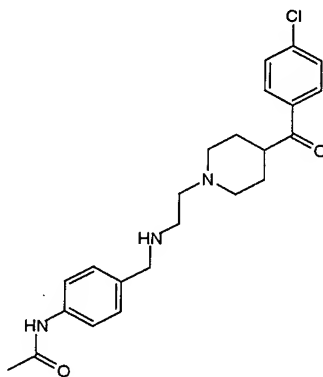
**Ethyl 3-[(2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl)-amino)methyl]cyclohexanecarboxylate**



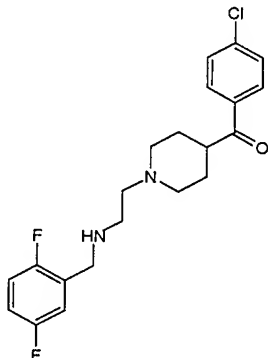
5 MS: APC1 (+ve) BP 435

**Example 144**

**N-{4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]phenyl}acetamide**

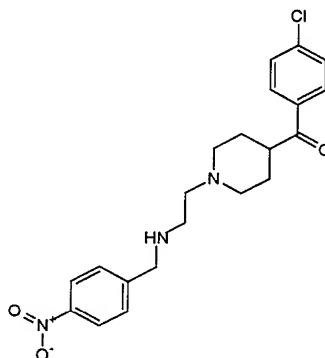


10 MS: APC1 (+ve) BP 414

**Example 145****(4-Chlorophenyl)(1-{2-[(2,5-difluorobenzyl)amino]ethyl}-4-piperidinyloxy)methanone**

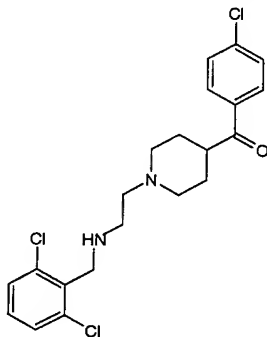
MS: APC1 (+ve) BP 393

5

**Example 146****(4-Chlorophenyl)(1-{2-[(4-nitrobenzyl)amino]ethyl}-4-piperidinyloxy)methanone**

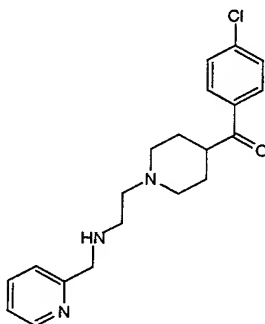
MS: APC1 (+ve) BP 402

10

**Example 147****(4-Chlorophenyl)(1-{2-[(2,6-dichlorobenzyl)amino]ethyl}-4-piperidiny]methanone**

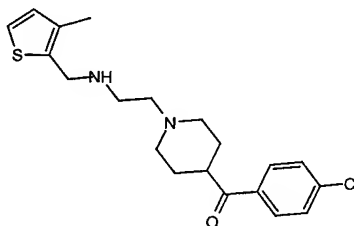
MS: APC1 (+ve) BP 425

5

**Example 148****(4-Chlorophenyl)(1-{2-[(2-pyridinylmethyl)amino]ethyl}-4-piperidiny]methanone**

MS: APC1 (+ve) BP 358

10

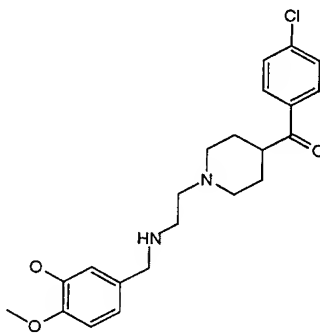
**Example 149****(4-Chlorophenyl)[1-(2-[[3-methyl-2-thienyl)methyl]amino]ethyl)-4-piperidiny]methanone**

15 MS: APC1 (+ve) BP 377



**Example 150**

**(4-Chlorophenyl)(1-{2-[(3-hydroxy-4-methoxybenzyl)amino]ethyl}-4-piperidiny)methanone**

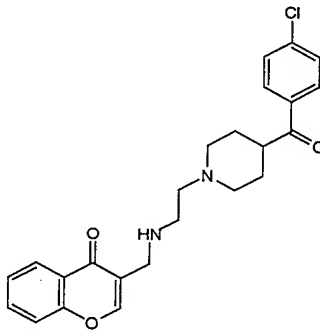


5

MS: APC1 (+ve) BP 403

**Example 151**

**3-[(2-[4-(4-Chlorobenzoyl)-1-piperidiny]ethyl)amino)methyl]-4H-chromen-4-one**

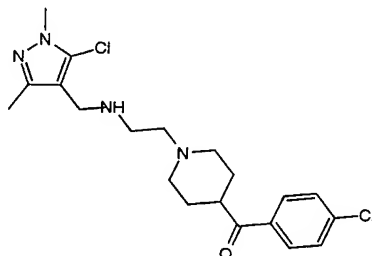


10

MS: APC1 (+ve) BP 425

**Example 152**

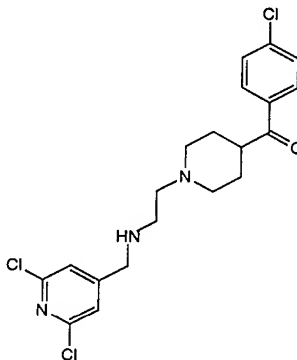
**[1-(2-[[[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino]ethyl]-4-piperidiny]l(4-chlorophenyl)methanone**



5 MS: APC1 (+ve) BP 409

**Example 153**

**(4-Chlorophenyl)[1-(2-[[[(2,6-dichloro-4-pyridinyl)methyl]amino]ethyl]-4-piperidiny]l)methanone**

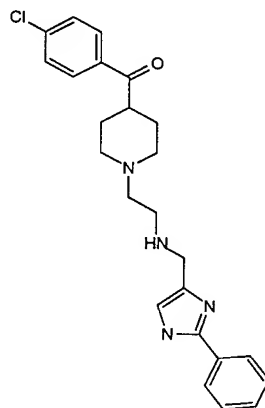


10

MS: APC1 (+ve) BP 428

**Example 154**

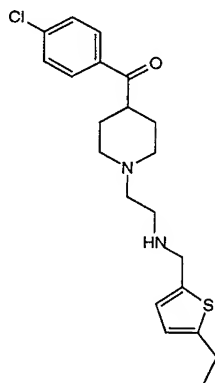
**(4-Chlorophenyl)[1-(2-{[(2-phenyl-1H-imidazol-4-yl)methyl]amino}ethyl)-4-piperidiny]methanone**



5 MS: APC1 (+ve) BP 423

**Example 155**

**(4-Chlorophenyl)[1-(2-{[(5-ethyl-2-thienyl)methyl]amino}ethyl)-4-piperidiny]methanone**

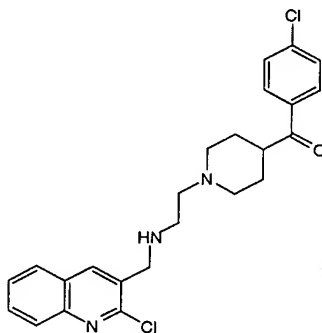


10

MS: APC1 (+ve) BP 391

**Example 156**

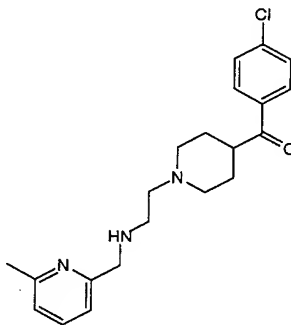
**(4-Chlorophenyl)[1-(2-[[2-chloro-3-quinolyl)methyl]amino}ethyl)-4-piperidiny]methanone**



5 MS: APC1 (+ve) BP 442

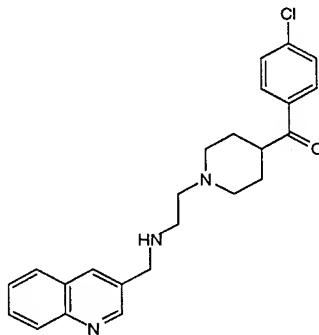
**Example 157**

**(4-Chlorophenyl)[1-(2-[[6-methyl-2-pyridinyl)methyl]amino}ethyl)-4-piperidiny]methanone**



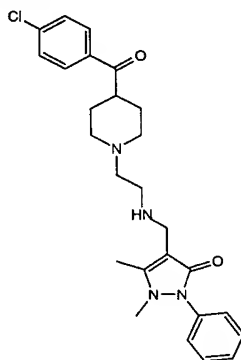
10

MS: APC1 (+ve) BP 372

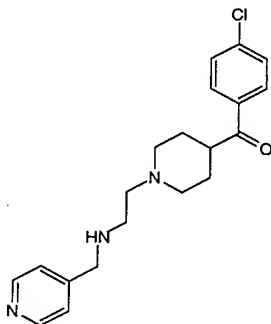
**Example 158****(4-Chlorophenyl)(1-{2-[(3-quinolinylmethyl)amino]ethyl}-4-piperidinyl)methanone**

MS: APC1 (+ve) BP 408

5

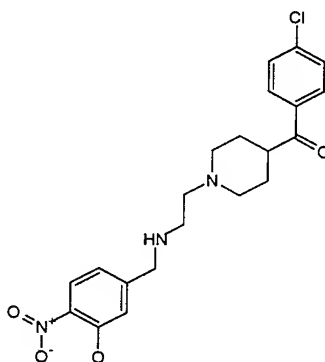
**Example 159****4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one**

10 MS: APC1 (+ve) BP 467

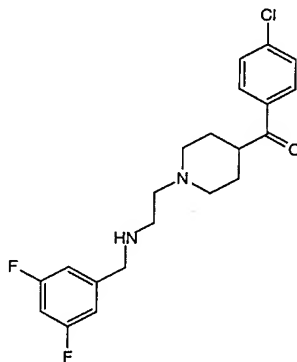
**Example 160****(4-Chlorophenyl)(1-{2-[(4-pyridinylmethyl)amino]ethyl}-4-piperidinyloxy)methanone**

MS: APC1 (+ve) BP 358

5

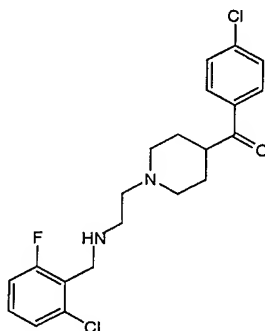
**Example 161****(4-Chlorophenyl)(1-{2-[(3-hydroxy-4-nitrobenzyl)amino]ethyl}-4-piperidinyloxy)methanone**

10 MS: APC1 (+ve) BP 418

**Example 162****(4-Chlorophenyl)(1-{2-[(3,5-difluorobenzyl)amino]ethyl}-4-piperidinyloxy)methanone**

MS: APC1 (+ve) BP 393

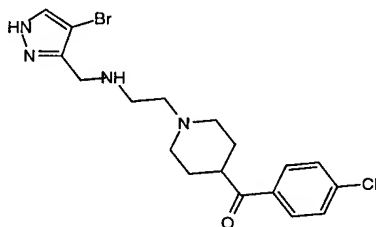
5

**Example 163****(1-{2-[(2-Chloro-6-fluorobenzyl)amino]ethyl}-4-piperidinyloxy)(4-chlorophenyl)methanone**

10 MS: APC1 (+ve) BP 409

**Example 164**

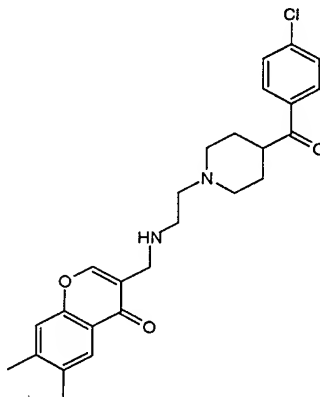
**[1-(2-[[4-Bromo-1H-pyrazol-3-yl)methyl]amino}ethyl)-4-piperidiny]l(4-chlorophenyl)methanone**



5 MS: APC1 (+ve) BP 427

**Example 165**

**3-[(2-[4-(4-Chlorobenzoyl)-1-piperidiny]ethyl)amino)methyl]-6,7-dimethyl-4H-chromen-4-one**



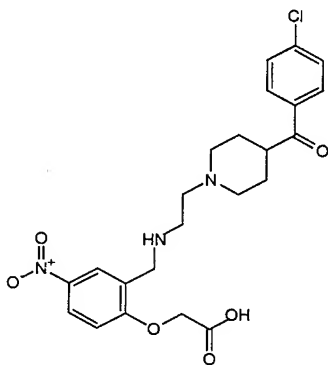
10

MS: APC1 (+ve) BP 453



**Example 166**

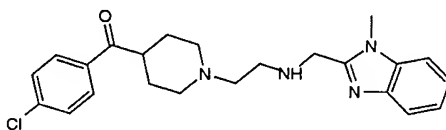
**2-{2-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4-nitrophenoxy}acetic acid**



5 MS: APC1 (+ve) BP 476

**Example 167**

**(4-Chlorophenyl)[1-(2-[(1-methyl-1H-benzimidazol-2-yl)methyl]amino)ethyl]-4-piperidinyl]methanone**



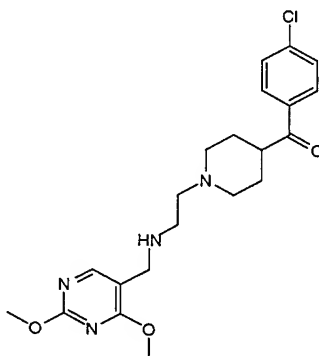
10

MS: APC1 (+ve) BP 411

**Example 168**

**(4-Chlorophenyl)[1-(2-[(2,4-dimethoxy-5-pyrimidinyl)methyl]amino)ethyl]-4-piperidinyl]methanone**

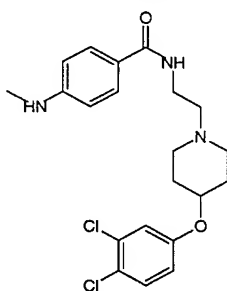
15



MS: APC1 (+ve) BP 419

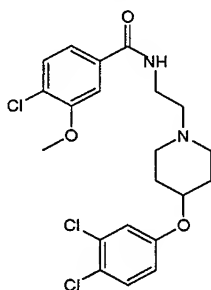
The compounds of following Examples 169 to 209 were prepared by methods analogous to the method of Example 2.

5

**Example 169****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(methylamino)benzamide**

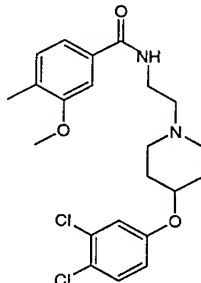
MS: APC1 (+ve) BP 422

10

**Example 170****4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide**

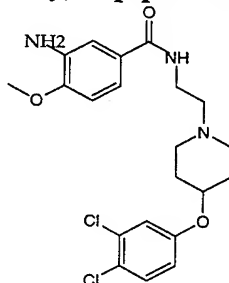
MS: APC1 (+ve) BP 459

15

**Example 171****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxy-4-methylbenzamide**

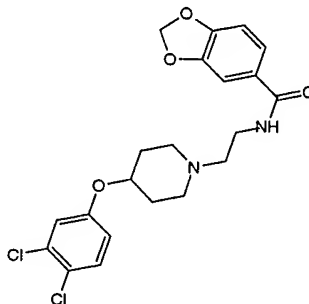
MS: APC1 (+ve) BP 437

5

**Example 172****3-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide**

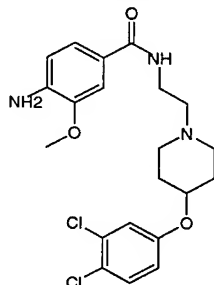
MS: APC1 (+ve) BP 438

10

**Example 173****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzodioxole-5-carboxamide**

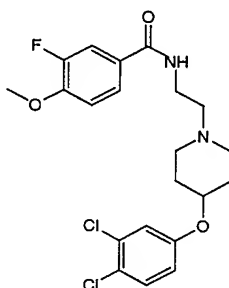
MS: APC1 (+ve) BP 437

15

**Example 174****4-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide**

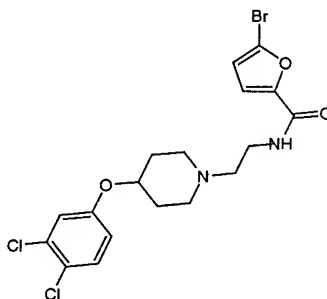
MS: APC1 (+ve) BP 438

5

**Example 175****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluoro-4-methoxybenzamide**

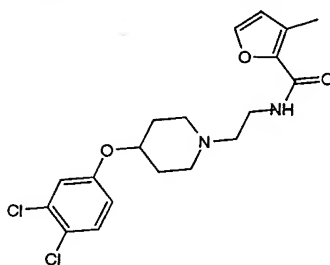
MS: APC1 (+ve) BP 441

10

**Example 176****5-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide**

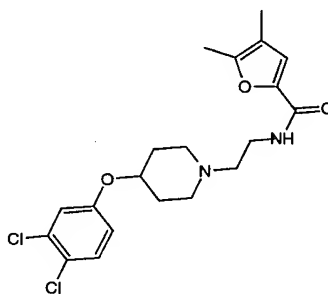
MS: APC1 (+ve) BP 463

15

**Example 177****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methyl-2-furamide**

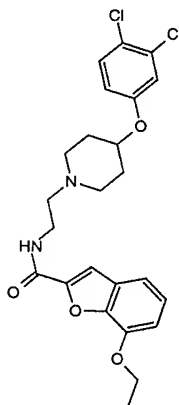
MS: APC1 (+ve) BP 397

5

**Example 178****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,5-dimethyl-2-furamide**

MS: APC1 (+ve) BP 411

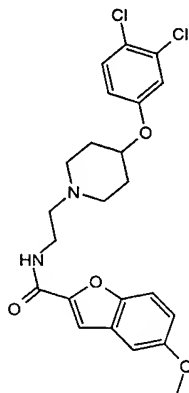
10

**Example 179****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-ethoxy-1-benzofuran-2-carboxamide**

MS: APC1 (+ve) BP 477

**Example 180**

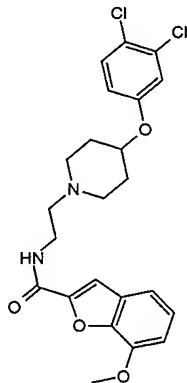
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-1-benzofuran-2-carboxamide**



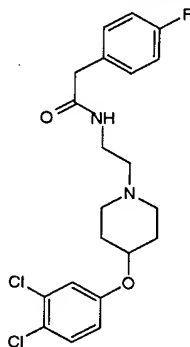
MS: APC1 (+ve) BP 463

**Example 181**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methoxy-1-benzofuran-2-carboxamide**

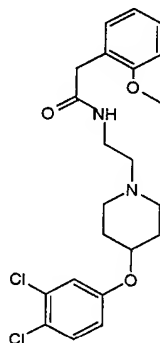


MS: APC1 (+ve) BP463

**Example 182****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-fluorophenyl)acetamide**

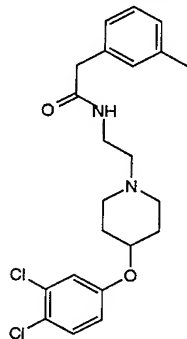
MS: APC1 (+ve) BP 425

5

**Example 183****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methoxyphenyl)acetamide**

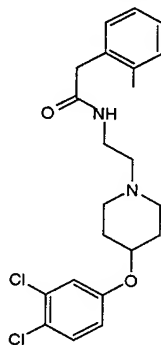
MS: APC1 (+ve) BP 437

10

**Example 184****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methylphenyl)acetamide**

MS: APC1 (+ve) BP421

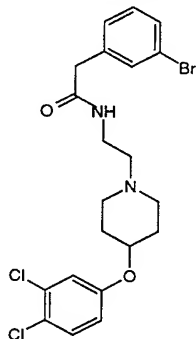
5

**Example 185****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methylphenyl)acetamide**

MS: APC1 (+ve) BP 421

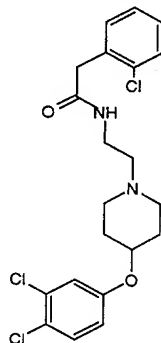
10



**Example 186****2-(3-Bromophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

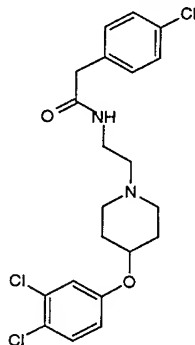
MS: APC1 (+ve) BP 487

5

**Example 187****2-(2-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

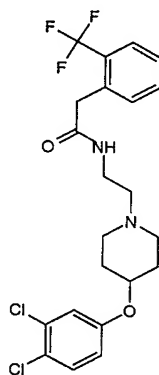
MS: APC1 (+ve) BP 441

10

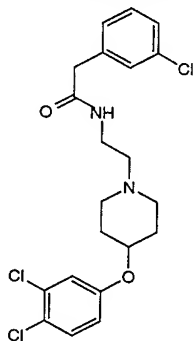
**Example 188****2-(4-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

MS: APC1 (+ve) BP 443

5

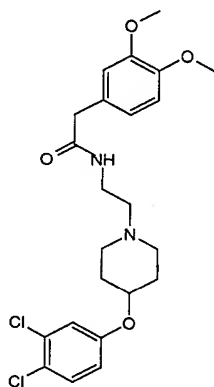
**Example 189****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(trifluoromethyl)phenyl]acetamide**

10 MS: APC1 (+ve) BP 475

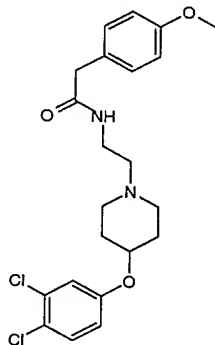
**Example 190****2-(3-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

MS: APC1 (+ve) BP441

5

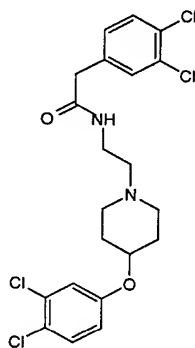
**Example 191****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dimethoxyphenyl)acetamide**

10 MS: APC1 (+ve) BP467

**Example 192****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methoxyphenyl)acetamide**

MS: APC1 (+ve) BP 437

5

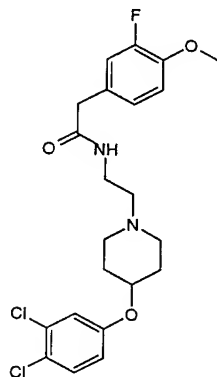
**Example 193****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dichlorophenyl)acetamide**

MS: APC1 (+ve) BP 477

10

**Example 194**

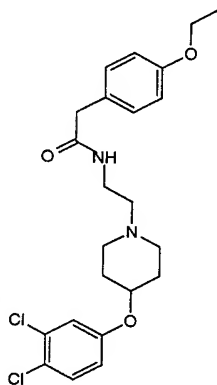
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-fluoro-4-methoxyphenyl)acetamide**



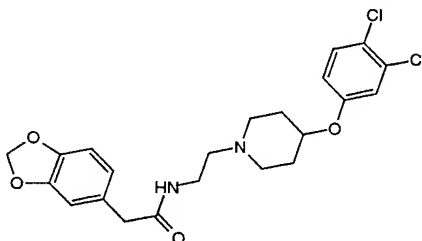
5 MS: APC1 (+ve) BP 455

**Example 195**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-ethoxyphenyl)acetamide**

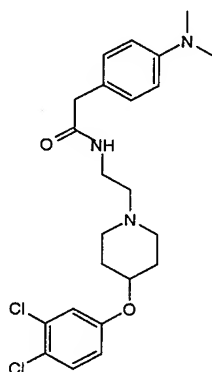


10 MS: APC1 (+ve) BP 451

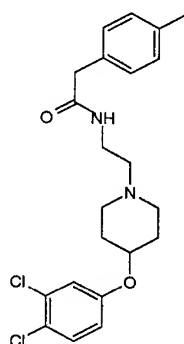
**Example 196****2-(1,3-Benzodioxol-5-yl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

MS: APC1 (+ve) BP451

5

**Example 197****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[4-(dimethylamino)phenyl]acetamide**

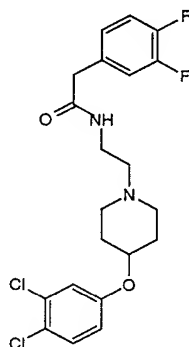
10 MS: APC1 (+ve) BP 450

**Example 198****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methylphenyl)acetamide**

MS: APC1 (+ve) BP 421

### Example 199

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-difluorophenyl)acetamide**

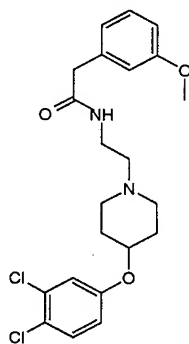


5

MS: APC1 (+ve) BP 443

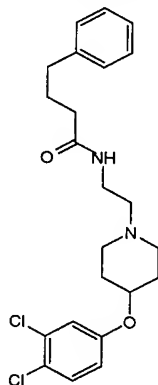
### Example 200

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methoxyphenyl)acetamide**



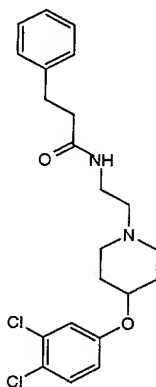
10

MS: APC1 (+ve) BP 437

**Example 201****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenylbutanamide**

MS: APC1 (+ve) BP 435

5

**Example 202****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenylpropanamide**

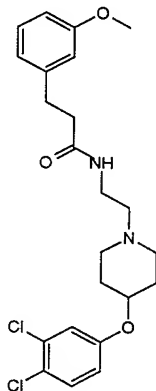
MS: APC1 (+ve) BP 421

10



**Example 203**

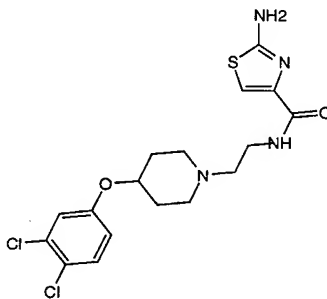
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(3-methoxyphenyl)propanamide**



5 MS: APC1 (+ve) BP 451

**Example 204**

**2-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-carboxamide**



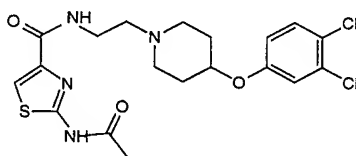
10

MS: APC1 (+ve) BP 416

**Example 205**

**2-(Acetylamino)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-carboxamide**

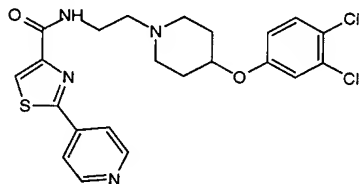
15



MS: APC1 (+ve) BP 457

**Example 206**

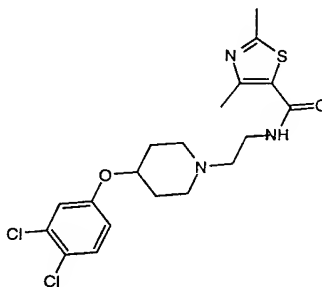
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-pyridinyl)-1,3-thiazole-4-**  
**carboxamide**



MS: APC1 (+ve) BP 477

**Example 207**

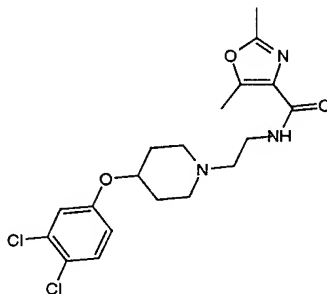
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-dimethyl-1,3-thiazole-5-**  
**carboxamide**



MS: APC1 (+ve) BP 428

**Example 208**

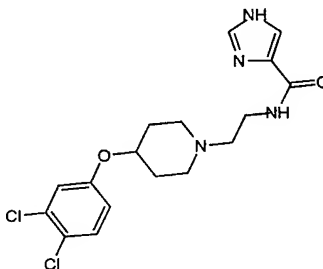
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,5-dimethyl-1,3-oxazole-4-carboxamide**



5 MS: APC1 (+ve) BP 412

**Example 209**

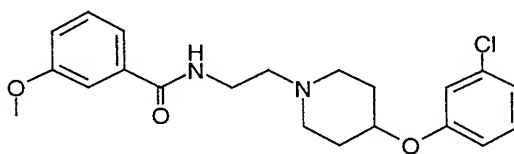
**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-imidazole-4-carboxamide**



10 MS: APC1 (+ve) BP 385.

**Example 210**

**N-{2-[4-(3,4-Chlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride**



15

**(i) 2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethylamine trifluoroacetate**

Prepared by the method of Example 1 steps (i) to (iv) using 3-chlorophenol to give the product as an oil (0.5 g) which was used directly in the next step without further purification.

5

**(ii) N-{2-[4-(3,4-Chlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride**

The product of step (i) above (0.3g) was dissolved in dichloromethane (490ml), triethylamine (4 equiv) and 3-methoxybenzoyl chloride (1 equiv) were added. After 72 hours at room temperature, water was added, the organic phase separated, dried and concentrated to a gum. The product was dissolved in dichloromethane and treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.1 g).

10

Melting point: 175-176 °C

MS: APCI(+ve): 389(M+H)

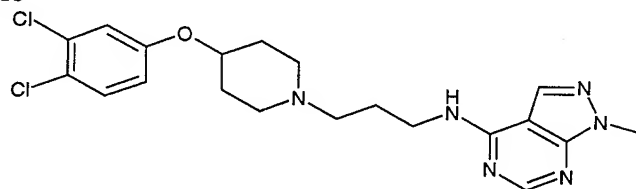
15

<sup>1</sup>H NMR: δ(DMSO) 8.87 (t, 1H), 7.5 (m, 2H), 7.42 (m, 1H), 7.32 (m, 1H), 7.13 (m, 2H), 6.98 (m, 2H), 4.82 (m, 1/2H), 4.61 (m, 1/2H), 3.81 (s, 3H), 3.69 (m, 3H), 3.68 (m, 3H), 3.47 (m, 1H), 3.13-3.22 (m, 4H), 2.27 (m, 1H), 2.14 (m, 1H), 2.03 (m, 1H), 1.90 (m, 1H)

**Example 211**

20

**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine**



**(i) 2-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1H-isoindole-1,3(2H)-dione**

A solution of the product from Example 1 step (ii) (2.0g), 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione (1.61g) and triethylamine (2.5ml) in dichloromethane (40ml) was heated under reflux for 48h. The reaction mixture was partitioned between ethyl

25

acetate/water, the organic layer dried and evaporated under reduced pressure. Purification was by chromatography eluting with 4% methanol/dichloromethane. Yield 0.839g

MS: APCI(+ve) 433 (M+1)

5

**(ii) 3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propylamine, dihydrochloride salt**

The product from step (i) (0.83g) and hydrazine hydrate (0.1ml) in ethanol was heated under reflux for 6h. The precipitate was filtered off and partitioned between 2M hydrochloric acid and dichloromethane, the solid was filtered off and the aqueous layer  
10 basified with aqueous potassium hydroxide solution and extracted with dichloromethane. The organic layer was dried, evaporated under reduced pressure and the dihydrochloride salt formed using ethereal hydrogen chloride. Yield 0.28g

<sup>1</sup>H NMR: δ(DMSO-d<sub>6</sub>) 11.11(br s, 1H), 8.13(br s, 3H), 7.56 (d, 1H), 7.37(s, 1H), 7.10-  
15 7.06(br m, 1H), 4.84(br s, 0.5H), 4.65(br s, 0.5H), 3.60-2.90(m, 8H), 2.24-2.01(m, 6H).

**(iii) N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine**

The product from step (ii) (0.08g), 4-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine  
20 (0.054g) and diisopropylethylamine (0.082g) in 1-methyl-2-pyrrolidinone (2ml) was heated at 50°C for 3h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried and the solvent removed under reduced pressure. Purification was by chromatography eluting with 9% methanol/dichloromethane. Yield 0.052g

25 MS: APCI(+ve) 435 (M+1)

<sup>1</sup>H NMR: δ(DMSO-d<sub>6</sub>) 8.25-8.22(m, 2H), 8.07(s, 1H), 7.49(d, 1H), 7.25(d, 1H), 6.97(dd, 1H), 4.46-4.42(m, 1H), 3.88(s, 3H), 3.49(q, 2H), 2.70-2.66(m, 2H), 2.40-2.36(m, 2H), 2.27-2.22(m, 2H), 1.92-1.88(m, 2H), 1.81-1.74(m, 2H), 1.62-1.59(m, 2H).

Melting point: 120-124°C

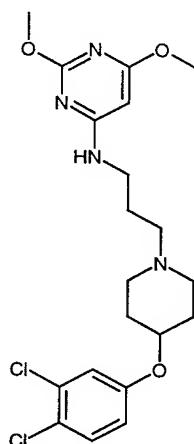
30

**Examples 212-255**

The product from Example 211 step (ii) (1.5mg), the appropriate activated halo aromatic (1.25 equivalents), diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrrolidinone (0.15ml) were heated at 100°C for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

**Example 212**

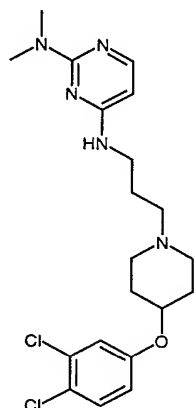
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2,6-dimethoxy-4-pyrimidinamine**



MS: APCI(+ve) 441 (M+1)

**Example 213**

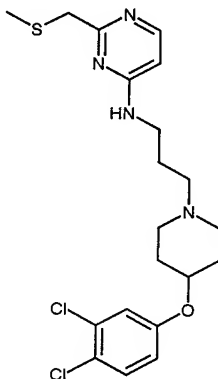
**N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine**



MS: APCI(+ve) 424 (M+1)

### Example 214

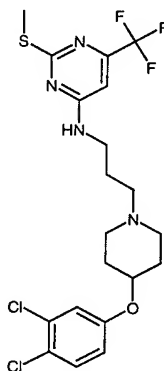
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine



MS: APCI(+ve) 441 (M+1)

### Example 215

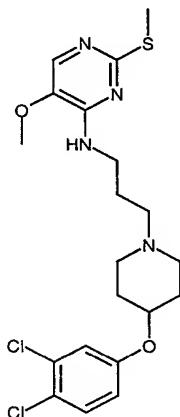
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinamine



MS: APCI(+ve) 495 (M+1)

**Example 216**

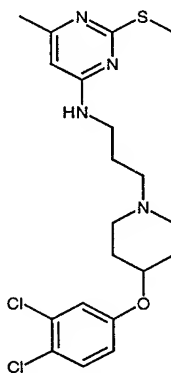
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine**



5 MS: APCI(+ve) 457 (M+1)

**Example 217**

**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine**



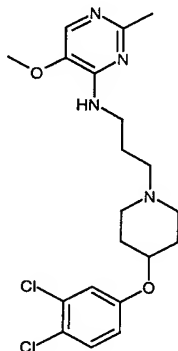
10

MS: APCI(+ve) 441 (M+1)



**Example 218**

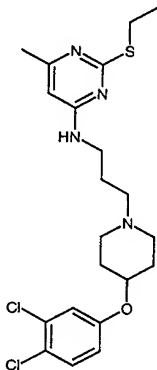
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-methyl-4-pyrimidinamine**



5 MS: APCI(+ve) 425 (M+1)

**Example 219**

**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(ethylsulfanyl)-6-methyl-4-pyrimidinamine**



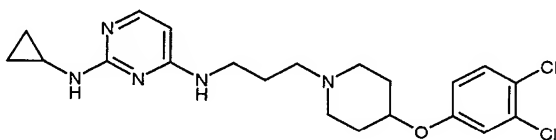
10

MS: APCI(+ve) 455 (M+1)

**Example 220**

**N~2~-Cyclopropyl-N~4~-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2,4-pyrimidinediamine**

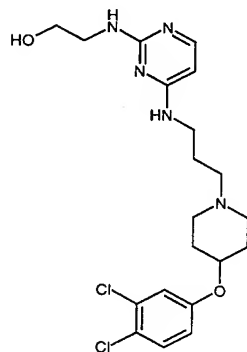
15



MS: APCI(+ve) 436 (M+1)

**Example 221**

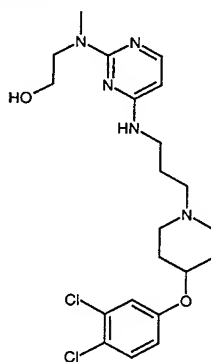
**2-[[4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-2-pyrimidinyl]amino]-1-ethanol**



MS: APCI(+ve) 440 (M+1)

**Example 222**

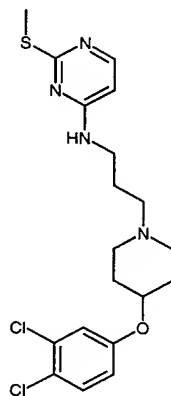
**2-[[4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-2-pyrimidinyl](methylamino)-1-ethanol**



MS: APCI(+ve) 454 (M+1)

**Example 223**

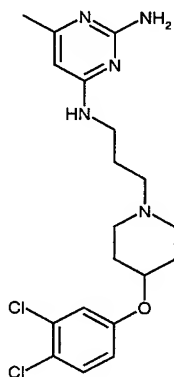
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-4-pyrimidinamine**



5 MS: APCI(+ve) 427 (M+1)

**Example 224**

**N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2,4-pyrimidinediamine**

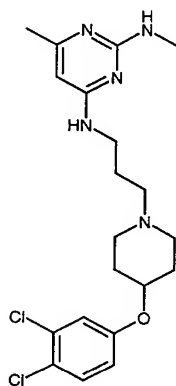


10

MS: APCI(+ve) 410 (M+1)

**Example 225**

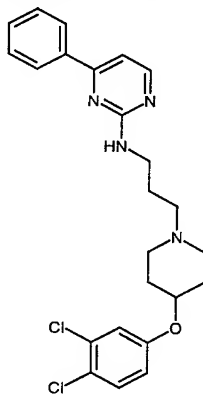
**N-{4-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-N-2,6-dimethyl-2,4-pyrimidinediamine}**



5 MS: APCI(+ve) 424 (M+1)

**Example 226**

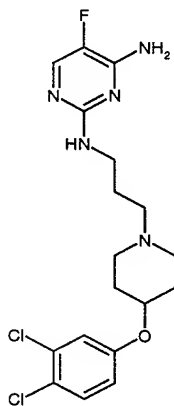
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-phenyl-2-pyrimidinamine**



10 MS: APCI(+ve) 457 (M+1)

**Example 227**

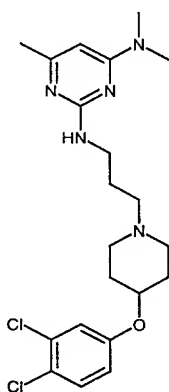
**N-2-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-fluoro-2,4-pyrimidinediamine**



5 MS: APCI(+ve) 414 (M+1)

**Example 228**

**N-2-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N-4,N-4,6-trimethyl-2,4-pyrimidinediamine**

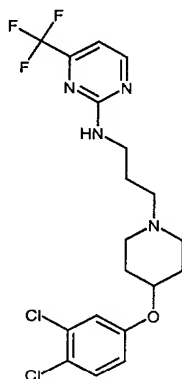


10

MS: APCI(+ve) 438 (M+1)

**Example 229**

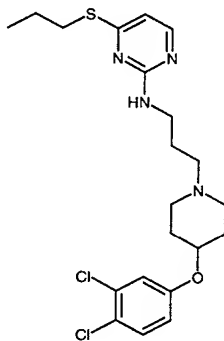
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(trifluoromethyl)-2-pyrimidinamine**



5 MS: APCI(+ve) 449 (M+1)

**Example 230**

**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(propylsulfanyl)-2-pyrimidinamine**

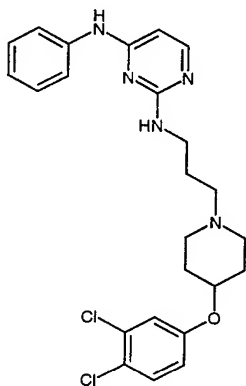


10

MS: APCI(+ve) 455 (M+1)

**Example 231**

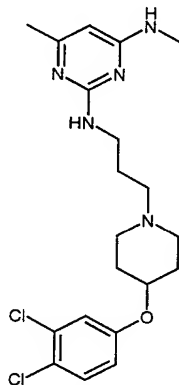
**N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~-phenyl-2,4-pyrimidinediamine**



5 MS: APCI(+ve) 472 (M+1)

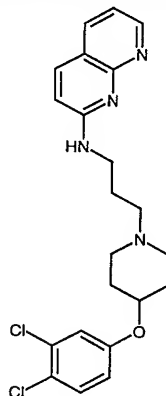
**Example 232**

**N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,6-dimethyl-2,4-pyrimidinediamine**



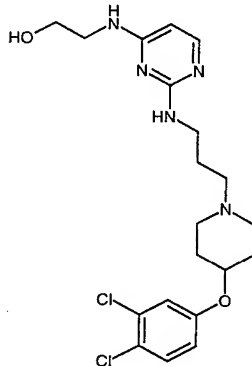
10

MS: APCI(+ve) 424 (M+1)

**Example 233****N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}[1,8]naphthyridin-2-amine**

MS: APCI(+ve) 431 (M+1)

5

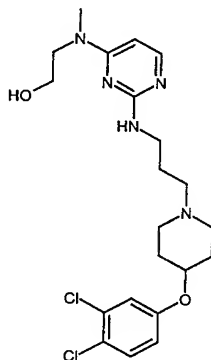
**Example 234****2-{{2-([3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]amino)-4-pyrimidinyl}amino}-1-ethanol**

10 MS: APCI(+ve) 440 (M+1)



**Example 235**

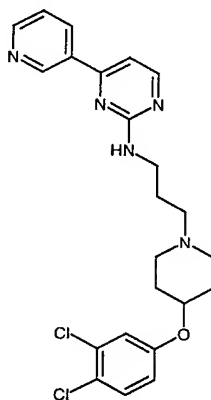
**2-[[2-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-4-pyrimidinyl](methyl)amino]-1-ethanol**



5 MS: APCI(+ve) 454 (M+1)

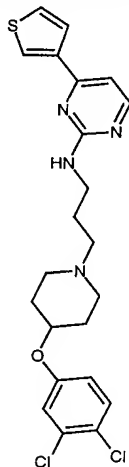
**Example 236**

**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-pyridinyl)-2-pyrimidinamine**



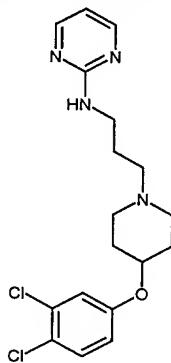
10

MS: APCI(+ve) 458 (M+1)

**Example 237****N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-thienyl)-2-pyrimidinamine**

MS: APCI(+ve) 463 (M+1)

5

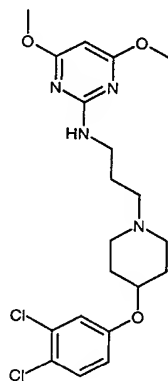
**Example 238****N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrimidinamine**

MS: APCI(+ve) 381 (M+1)

10

**Example 239**

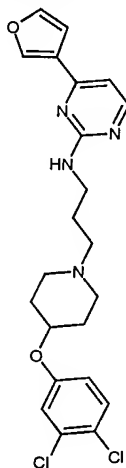
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4,6-dimethoxy-2-pyrimidinamine**



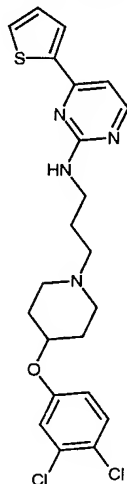
5 MS: APCI(+ve) 441 (M+1)

**Example 240**

**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-furyl)-2-pyrimidinamine**

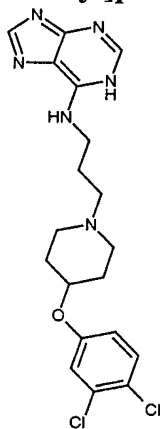


10 MS: APCI(+ve) 447 (M+1)

**Example 241****N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(2-thienyl)-2-pyrimidinamine**

MS: APCI(+ve) 463 (M+1)

5

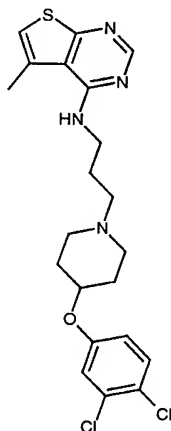
**Example 242****N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1H-purin-6-amine**

MS: APCI(+ve) 421 (M+1)

10

**Example 243**

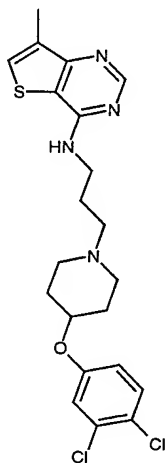
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methylthieno[2,3-d]pyrimidin-4-amine**



5 MS: APCI(+ve) 451 (M+1)

**Example 244**

**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-7-methylthieno[3,2-d]pyrimidin-4-amine**

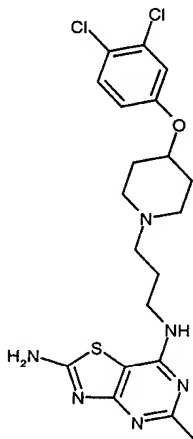


10

MS: APCI(+ve) 451 (M+1)

**Example 245**

**N~7~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine**

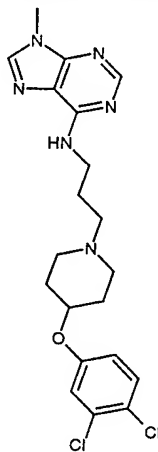


5

MS: APCI(+ve) 467 (M+1)

**Example 246**

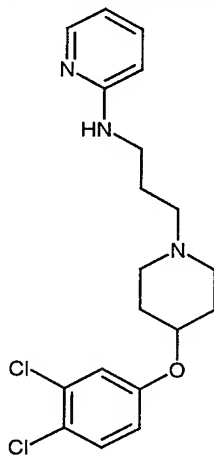
**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-9-methyl-9H-purin-6-amine**



10

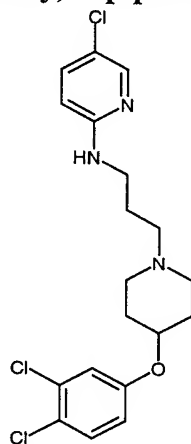
MS: APCI(+ve) 435 (M+1)

145

**Example 247****N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine**

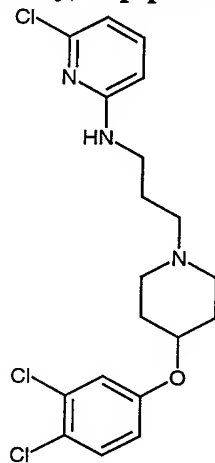
MS: APCI(+ve) 379 (M+1)

5

**Example 248****5-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine**

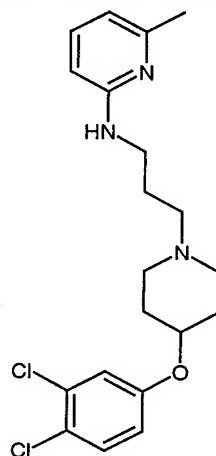
MS: APCI(+ve) 414 (M+1)

10

**Example 249****6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidiny]propyl}-2-pyridinamine**

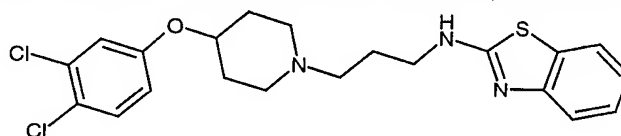
MS: APCI(+ve) 414 (M+1)

5

**Example 250****N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidiny]propyl}-6-methyl-2-pyridinamine**

MS: APCI(+ve) 494 (M+1)

10

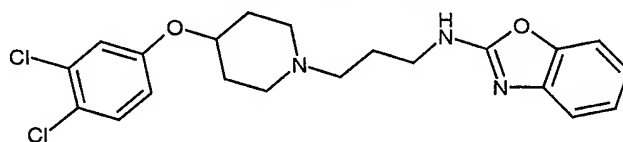
**Example 251****N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidiny]propyl}-1,3-benzothiazol-2-amine**



MS: APCI(+ve) 436 (M+1)

### Example 252

**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzoxazol-2-amine**

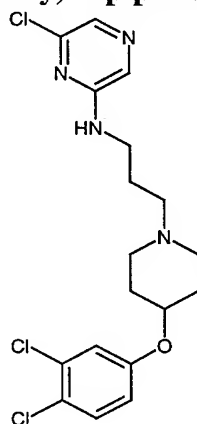


5

MS: APCI(+ve) 420 (M+1)

### Example 253

**6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrazinamine**



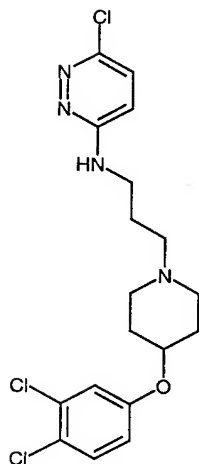
10

MS: APCI(+ve) 415 (M+1)

### Example 254

**6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-3-pyridazinamine**

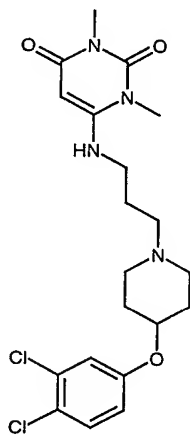
148



MS: APCI(+ve) 417 (M+1)

### Example 255

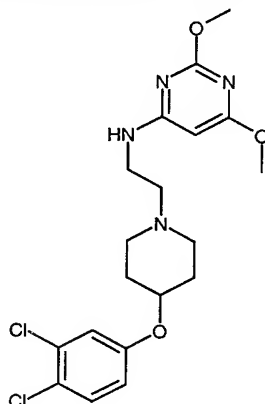
5 **6-((3-[4-(3,4-Dichlorophenoxy)-1-piperidiny]propyl)amino)-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione**



MS: APCI(+ve) 441 (M+1)

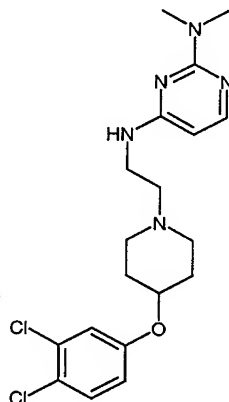
### 10 Examples 256-292

The product from Example 1 step (iv) (2.07mg), the appropriate activated halo aromatic (1.25 equivalents), diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrrolidinone (0.15ml) were heated at 100°C for 24h.. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

**Example 256****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,6-dimethoxy-4-pyrimidinamine**

MS: APCI(+ve) 427 (M+1)

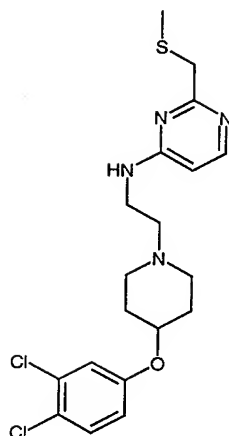
5

**Example 257****N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine**

10 MS: APCI(+ve) 410 (M+1)

**Example 258****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[(methylsulfonyl)methyl]-4-pyrimidinamine**

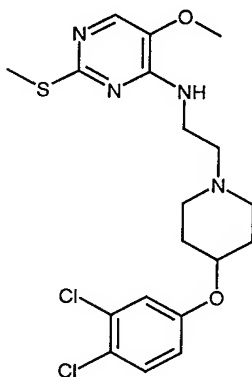
150



MS: APCI(+ve) 427 (M+1)

**Example 259**

5 **N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine**

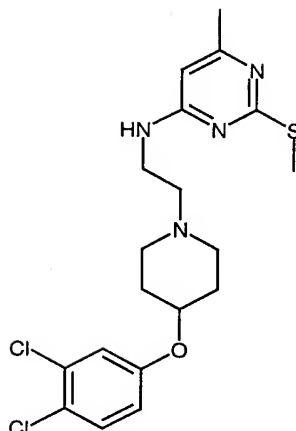


MS: APCI(+ve) 443 (M+1)

10 **Example 260**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine**

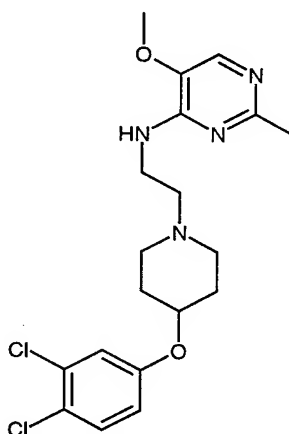
151



MS: APCI(+ve) 427 (M+1)

5 **Example 261**

**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-methyl-4-pyrimidinamine**

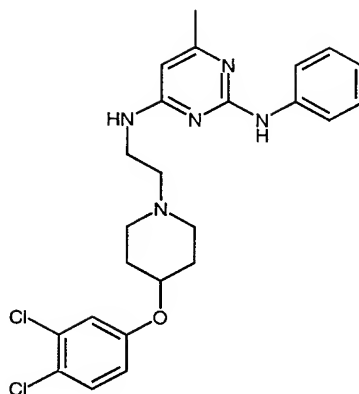


MS: APCI(+ve) 411 (M+1)

10

**Example 262**

**N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-N~2~-phenyl-2,4-pyrimidinediamine**



MS: APCI(+ve) 472 (M+1)

### Pharmacological Analysis

5

#### Calcium flux [ $\text{Ca}^{2+}$ ]<sub>i</sub> assay

##### a) Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells  
10 were resuspended ( $5 \times 10^6 \text{ ml}^{-1}$ ) and loaded with  $5 \mu\text{M}$  FLUO-3/AM + Pluronic F127  $2.2 \mu\text{l/ml}$  (Molecular Probes) in low potassium solution (LKS; NaCl 118mM,  $\text{MgSO}_4$  0.8mM, glucose 5.5mM,  $\text{Na}_2\text{CO}_3$  8.5mM, KCl 5mM, HEPES 20mM,  $\text{CaCl}_2$  1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at  $2.5 \times 10^6 \text{ ml}^{-1}$ . The cells were then transferred to  
15 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with  $5 \mu\text{M}$  fibronectin for two hours) at 100ml/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200 $\mu\text{l}$ ; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final  
20 concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an  $A_{50}$  concentration of eotaxin and the transient increase in fluo-3 fluorescence ( $I_{\text{Ex}} = 490\text{nm}$  and  $I_{\text{Em}} = 520\text{nm}$ ) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

**b) Human monocytes**

Human monocytes were isolated from EDTA anticoagulated peripheral blood as previously described (Cunoosamy & Holbrook, J. Leukocyte Biology, 1998, S2, 13). Cells were  
5 resuspended ( $5 \times 10^6 \text{ ml}^{-1}$ ) in LKS and loaded with  $5 \mu\text{M}$  FLUO-3/AM + Pluronic F127  
2.2  $\mu\text{l/ml}$  (Molecular Probes) for one hour at room temperature. After loading, cells were  
centrifuged at 200g for 5min and resuspended in LKS at  $0.5 \times 10^6 \text{ ml}^{-1}$ . The cells were then  
transferred to 96 well FLIPr plates (Costar). To each well 100  $\mu\text{l}$  of cells were added at a  
concentration of  $0.5 \times 10^6 \text{ ml}^{-1}$ . The plates were centrifuged (200g; 5 mins; room  
10 temperature) to allow the cells to adhere. After centrifugation the cells were washed twice  
with LKS (200  $\mu\text{l}$ ; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final  
concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an  $A_{50}$   
15 concentration of MIP-1 $\alpha$  and the transient increase in fluo-3 fluorescence ( $I_{\text{Ex}} = 490\text{nm}$  and  
 $I_{\text{Em}} = 520\text{nm}$ ) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular  
Devices, Sunnyvale, U.S.A.).

The compounds of the Examples were found to be antagonists of the eotaxin mediated  
20  $[\text{Ca}^{2+}]_i$  in human eosinophils and/or antagonists of the MIP-1 $\alpha$  mediated  $[\text{Ca}^{2+}]_i$  in human  
monocytes.

**Human eosinophil chemotaxis**

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as  
25 previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells  
were resuspended at  $10 \times 10^6 \text{ ml}^{-1}$  in RPMI containing 200 IU/ml penicillin, 200  $\mu\text{g/ml}$   
streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700  $\mu\text{l}$ ) were pre-incubated for 15 mins at 37° C with 7  $\mu\text{l}$  of either vehicle or  
30 compound (100x required final concentration in 10% DMSO). The chemotaxis plate

(ChemoTx, 3µm pore, Neuroprobe) was loaded by adding 28µl of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 µl of eosinophil suspension were added to the top of the filter. The  
5 plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO<sub>2</sub> atmosphere to allow chemotaxis.

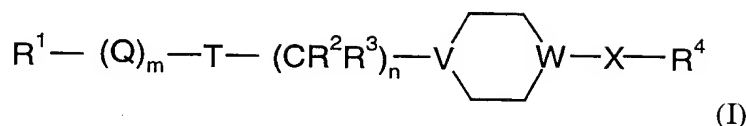
The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS)  
10 containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 µl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the  
15 supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Certain compounds of the Examples were found to be antagonists of the eotaxin mediated  
20 human eosinophil chemotaxis.



## CLAIMS

1. A compound of general formula



wherein:

$R^1$  represents a  $C_1$ - $C_{12}$  alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylthio and  $C_1$ - $C_6$  alkoxycarbonyl groups, or

$R^1$  represents a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one or more substituents independently selected from halogen atoms, and cyano, nitro, hydroxyl,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxycarbonyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy,  $-NR^5R^6$ ,  $C_3$ - $C_6$  cycloalkylamino,  $C_1$ - $C_6$  alkylthio,  $C_1$ - $C_6$  alkylthio $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylcarbonylamino,  $-C(O)NR^7R^8$ , sulphonamido, (di) $C_1$ - $C_6$  alkylsulphonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and  $C(O)R^9$ -substituted  $C_1$ - $C_6$  alkyl or  $C_1$ - $C_6$  alkoxy groups;

$m$  is 0 or 1;

$Q$  represents a group  $OCH_2$ ,  $C_1$ - $C_4$  alkylene or  $C_2$ - $C_4$  alkenylene;

$T$  represents a group  $C(O)NH$ , or when  $m$  is 0,  $T$  may additionally represent a bond or a group  $NH$ , or when  $m$  is 1 and  $Q$  represents  $C_1$ - $C_4$  alkylene,  $T$  may additionally represent a group  $NH$ ;

$n$  is 1, 2, 3 or 4;

each  $R^2$  independently represents a hydrogen atom or a  $C_1$ - $C_4$  alkyl group;

each  $R^3$  independently represents a hydrogen atom or a  $C_1$ - $C_4$  alkyl group;

$V$  represents a nitrogen atom;

W represents a nitrogen atom or a group CH;

X represents an oxygen atom or a group C(O), CH(OH), NH or N(C<sub>1</sub>-C<sub>6</sub> alkyl), provided that when W represents a nitrogen atom, then X represents C(O);

R<sup>4</sup> represents a phenyl group optionally substituted by one or more substituents

5 independently selected from halogen atoms, and amino, nitro, cyano, sulphonyl, sulphonamido, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy and

C<sub>1</sub>-C<sub>6</sub> alkylsulphonyl groups;

R<sup>5</sup> and R<sup>6</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl or hydroxyC<sub>1</sub>-C<sub>6</sub> alkyl group, or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are

10 attached form a 4- to 7-membered saturated heterocyclic ring;

R<sup>7</sup> and R<sup>8</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group; and

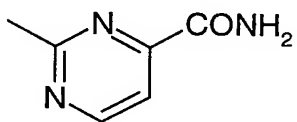
R<sup>9</sup> represents a hydroxyl or -NR<sup>7</sup>R<sup>8</sup> group;

with the provisos that

(a) when m is 0, T is CONH, n is 2, 3 or 4 and each R<sup>2</sup> and R<sup>3</sup> represents hydrogen, W is 15 CH, X is C(O) or CH(OH) and R<sup>1</sup> represents a substituted 3- to 10-membered unsaturated ring system, then the one or more substituents in the ring system do not include hydroxyl, halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy or C<sub>1</sub>-C<sub>6</sub> haloalkoxy, and

(b) when W is N, X is C(O), R<sup>4</sup> represents 3-trifluoromethylphenyl, m is 0 and T is a bond, then R<sup>1</sup> and (CR<sup>2</sup>R<sup>3</sup>)<sub>n</sub> taken together do not represent a C<sub>1</sub>-C<sub>6</sub> alkyl group, and

20 (c) when W is CH, X is O, n is 2 or 3 and each R<sup>2</sup> and R<sup>3</sup> represents hydrogen, m is 0 and T is NH, then R<sup>1</sup> does not represent a group



or a pharmaceutically acceptable salt or solvate thereof.

25

2. A compound according to claim 1, wherein R<sup>1</sup> represents a C<sub>1</sub>-C<sub>10</sub> alkyl group optionally substituted by one or two substituents independently selected from cyano, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio and C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl groups, or

$R^1$  represents a 3- to 10-membered saturated or unsaturated ring system comprising up to two ring carbon atoms that form carbonyl groups and comprising up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one, two or three substituents independently selected from halogen atoms, and cyano, nitro, hydroxyl,  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkoxycarbonyl,  $C_1$ - $C_3$  haloalkyl,  $C_1$ - $C_3$  haloalkoxy,  $-NR^5R^6$ ,  $C_3$ - $C_6$  cycloalkylamino,  $C_1$ - $C_4$  alkylthio,  $C_1$ - $C_4$  alkylthio $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkylcarbonylamino,  $-C(O)NR^7R^8$ , phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and  $C(O)R^9$ -substituted  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkoxy groups.

3. A compound according to claim 1 or claim 2, wherein m is 1 and Q represents a group  $OCH_2$ ,  $C_1$ - $C_3$  alkylene or  $C_2$ - $C_3$  alkenylene.
4. A compound according to any one of claims 1 to 3, wherein T represents a group  $C(O)NH$ .
5. A compound according to any one of the preceding claims, wherein n is 2 or 3.
6. A compound according to any one of the preceding claims, wherein V represents a nitrogen atom and W represents a group CH.
7. A compound according to any one of the preceding claims, wherein X represents an oxygen atom or a group  $C(O)$  or NH.
8. A compound according to any one of the preceding claims, wherein  $R^4$  represents a phenyl group optionally substituted by one or two halogen atoms.
9. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, according to claim 1 being selected from:

- 4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-ethoxybenzamide hydrochloride,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-isopropoxybenzamide,  
5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-ethoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide hydrochloride,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethoxy)benzamide  
10 hydrochloride,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide hydrochloride,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide hydrochloride,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride,  
3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide hydrochloride,  
15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide hydrochloride,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-hydroxybenzamide hydrochloride,  
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-[2-(methylamino)-2-oxoethoxy]benzamide hydrochloride,  
20 2-[3-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl}-2,4-dioxo-3,4-dihydro-1(2H)-quinazolinyl]-N,N-dimethylacetamide hydrochloride,  
N-{2-[4-(3,4-Dichlorobenzoyl)-1-piperazinyl]ethyl}-3-methoxybenzamide hydrochloride,  
3,4-Dichloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}benzamide,  
4-Chloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide hydrochloride,  
25 N-7--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-9-methyl-9H-purin-6-amine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzothiazol-2-amine,  
30 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzoxazol-2-amine,

- 6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrazinamine,  
6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-pyridazinamine,  
6-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl} amino)-1,3-dimethyl-2,4(1H,3H)-  
pyrimidinedione,  
5 N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-4-methyl-  
benzamide, hydrochloride salt,  
N-{1-[4-(3,4-Dichloro-phenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-methoxy-  
benzamide, hydrochloride salt,  
N-{2-[4-(3,4-Dichloroanilino)-1-piperidinyl]ethyl}-3-methoxybenzamide dihydrochloride,  
10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-(3-methoxybenzyl)amine  
dihydrochloride,  
3-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methoxy-2,4(1H,3H)-  
quinazolinedione,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide,  
15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,  
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-nitrobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methylbenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-dinitrobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-iodobenzamide,  
25 4-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
4-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methylbenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-nitrobenzamide,  
3-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
30 3,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide,  
2,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methylbenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-iodobenzamide,  
5 4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-nitrobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-5-(trifluoromethyl)benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide,  
10 3,5-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)benzamide,  
3-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
2-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide,  
15 3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
2-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-difluorobenzamide,  
2,3-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-naphthamide,  
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-6-(trifluoromethyl)benzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-difluorobenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-thiophenecarboxamide,  
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide,  
Methyl 4-((2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl)amino)-4-oxobutanoate,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclobutanecarboxamide,  
30 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxyacetamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclohexanecarboxamide,  
 (E)-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide,  
 2-Chloro-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}nicotinamide,  
 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide,  
 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclopentanecarboxamide,  
 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenoxyacetamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}benzamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide,  
 4-(tert-Butyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}benzamide,  
 10 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methylbenzamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-nitrobenzamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-methylbenzamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-cyanobenzamide,  
 15 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-furamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-nitrobenzamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-naphthamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(2,3-dihydro-1,4-benzodioxin-2-yl)-1,3-  
 20 thiazole-4-carboxamide,  
 N~2~-Cyclopropyl-N~4~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-  
 pyrimidinediamine,  
 2-{[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-pyrimidinyl]amino}-1-  
 ethanol,  
 25 2-[[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-  
 pyrimidinyl](methyl)amino]-1-ethanol,  
 N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~-phenyl-2,4-  
 pyrimidinediamine,  
 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)-4-pyrimidinamine,  
 30 N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2,4-pyrimidinediamine,

- N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,6-dimethyl-2,4-pyrimidinediamine,  
2-Chloro-N~4~-cyclopropyl-N~6~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-pyrimidinediamine,  
5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenyl-2-pyrimidinamine,  
N~2~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)-2-pyrimidinamine,  
10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(propylsulfanyl)-2-pyrimidinamine,  
N~2~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~-phenyl-2,4-pyrimidinediamine,  
N~4~-Cyclopropyl-N~2~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine,  
15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}[1,8]naphthyridin-2-amine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-pyridinyl)-2-pyrimidinamine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrimidinamine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-dimethoxy-2-pyrimidinamine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-furyl)-2-pyrimidinamine,  
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-purin-6-amine,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methylthieno[2,3-d]pyrimidin-4-amine,  
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methylthieno[3,2-d]pyrimidin-4-amine,  
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-thiophenecarboxamide,  
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide,  
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide,  
30 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}cyclohexanecarboxamide,



- (E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide,  
 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-phenoxyacetamide,  
 (E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(4-nitrophenyl)-2-propenamide,  
 2-(1-Adamantyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}acetamide,  
 5 (4-Chlorophenyl)(1-{2-[(2-fluoro-4,5-dimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,  
 (4-Chlorophenyl)(1-{2-[(3,4,5-trimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,  
 (4-Chlorophenyl)(1-{2-[(3-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
 (4-Chlorophenyl){1-[2-(isobutylamino)ethyl]-4-piperidinyl}methanone,  
 10 4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4-ethylhexanenitrile,  
 (4-Chlorophenyl)(1-{2-[(7-hydroxy-3,7-dimethyloctyl)amino]ethyl}-4-piperidinyl)methanone,  
 (4-Chlorophenyl)[1-(2-{[(6-nitro-1,3-benzodioxol-5-yl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
 15 [1-(2-{[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone,  
 (4-Chlorophenyl)[1-(2-{[3-nitro-4-(2-pyridinylsulfanyl)benzyl]amino}ethyl)-4-piperidinyl]methanone,  
 (4-Chlorophenyl)[1-(2-{[(E)-3-(4-nitrophenyl)-2-propenyl]amino}ethyl)-4-piperidinyl]methanone,  
 20 (4-Chlorophenyl){1-[2-({[5-(3-nitrophenyl)-2-furyl]methyl}amino)ethyl]-4-piperidinyl}methanone,  
 (4-Chlorophenyl)[1-(2-{[5-nitro-2-(2-pyridinylsulfanyl)benzyl]amino}ethyl)-4-piperidinyl]methanone,  
 25 6-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-2-(methylsulfanyl)nicotinonitrile,  
 {1-[2-({[5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}amino)ethyl]-4-piperidinyl}(4-chlorophenyl)methanone,  
 (4-Chlorophenyl)[1-(2-{[3-(methylsulfanyl)butyl]amino}ethyl)-4-piperidinyl]methanone,

- (4-Chlorophenyl)[1-(2-{{(4-phenyl-4-piperidinyl)methyl}amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)[1-(2-{{(1-phenyl-1H-pyrazol-5-yl)methyl}amino}ethyl)-4-piperidinyl]methanone,
- 5 Ethyl 3-{{(2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl)-amino)methyl}cyclohexanecarboxylate,
- N-{{4-{{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl) amino)methyl}phenyl}acetamide,
- (4-Chlorophenyl)(1-{{2-[(2,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone,
- (4-Chlorophenyl)(1-{{2-[(4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,
- 10 (4-Chlorophenyl)(1-{{2-[(2,6-dichlorobenzyl)amino]ethyl}-4-piperidinyl)methanone,
- (4-Chlorophenyl)(1-{{2-[(2-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone,
- (4-Chlorophenyl)[1-(2-{{(3-methyl-2-thienyl)methyl}amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)(1-{{2-[(3-hydroxy-4-methoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,
- 15 3-{{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl) amino)methyl}-4H-chromen-4-one,
- [1-(2-{{(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl}amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone,
- (4-Chlorophenyl)[1-(2-{{(2,6-dichloro-4-pyridinyl)methyl}amino}ethyl)-4-piperidinyl]methanone,
- 20 (4-Chlorophenyl)[1-(2-{{(2-phenyl-1H-imidazol-4-yl)methyl}amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)[1-(2-{{(5-ethyl-2-thienyl)methyl}amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)[1-(2-{{(2-chloro-3-quinolinyl)methyl}amino}ethyl)-4-piperidinyl]methanone,
- 25 (4-Chlorophenyl)[1-(2-{{(6-methyl-2-pyridinyl)methyl}amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)(1-{{2-[(3-quinolinylmethyl)amino]ethyl}-4-piperidinyl)methanone,
- 4-{{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl) amino)methyl}-1,5-dimethyl-2-phenyl-
- 30 1,2-dihydro-3H-pyrazol-3-one,

- (4-Chlorophenyl)(1-{2-[(4-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone,  
(4-Chlorophenyl)(1-{2-[(3-hydroxy-4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
(4-Chlorophenyl)(1-{2-[(3,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone,  
(1-{2-[(2-Chloro-6-fluorobenzyl)amino]ethyl}-4-piperidinyl)(4-chlorophenyl)methanone,  
5 [1-(2-{[(4-Bromo-1H-pyrazol-3-yl)methyl]amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone,  
3-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-6,7-dimethyl-4H-chromen-4-one,  
2-{2-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4-nitrophenoxy}acetic  
10 acid,  
(4-Chlorophenyl)[1-(2-{[(1-methyl-1H-benzimidazol-2-yl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
(4-Chlorophenyl)[1-(2-{[(2,4-dimethoxy-5-pyrimidinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,  
15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(methylamino)benzamide,  
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxy-4-methylbenzamide,  
3-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzodioxole-5-carboxamide,  
20 4-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluoro-4-methoxybenzamide,  
5-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methyl-2-furamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,5-dimethyl-2-furamide,  
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-ethoxy-1-benzofuran-2-carboxamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-1-benzofuran-2-carboxamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methoxy-1-benzofuran-2-  
30 carboxamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-fluorophenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methylphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methylphenyl)acetamide,  
5 2-(3-Bromophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
2-(2-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
2-(4-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-  
(trifluoromethyl)phenyl]acetamide,  
10 2-(3-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dimethoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dichlorophenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-fluoro-4-  
15 methoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-ethoxyphenyl)acetamide,  
2-(1,3-Benzodioxol-5-yl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[4-  
(dimethylamino)phenyl]acetamide,  
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methylphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-difluorophenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methoxyphenyl)acetamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenylbutanamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenylpropanamide,  
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(3-methoxyphenyl)propanamide,  
2-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-carboxamide,  
2-(Acetylamino)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-  
carboxamide,  
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-pyridinyl)-1,3-thiazole-4-  
30 carboxamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-dimethyl-1,3-thiazole-5-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,5-dimethyl-1,3-oxazole-4-carboxamide,
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-imidazole-4-carboxamide,
- N-{2-[4-(3,4-Chlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide, hydrochloride salt,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- 10 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2,6-dimethoxy-4-pyrimidinamine,
- N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine,
- 15 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine,
- 20 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-methyl-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(ethylsulfanyl)-6-methyl-4-pyrimidinamine,
- 25 N~2~-Cyclopropyl-N~4~-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2,4-pyrimidinediamine,
- 2-{[4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-2-pyrimidinyl]amino}-1-ethanol,
- 2-[[4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-2-pyrimidinyl](methyl)amino]-1-ethanol,
- 30

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-4-pyrimidinamine,

N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2,4-pyrimidinediamine,

5 N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,6-dimethyl-2,4-pyrimidinediamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-phenyl-2-pyrimidinamine,

N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-fluoro-2,4-pyrimidinediamine,

10 N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(trifluoromethyl)-2-pyrimidinamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(propylsulfanyl)-2-pyrimidinamine,

15 N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~-phenyl-2,4-pyrimidinediamine,

N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,6-dimethyl-2,4-pyrimidinediamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}[1,8]naphthyridin-2-amine,

20 2-{[2-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-4-pyrimidinyl]amino}-1-ethanol,

2-[[2-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-4-pyrimidinyl](methyl)amino]-1-ethanol,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-pyridinyl)-2-pyrimidinamine,

25 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-thienyl)-2-pyrimidinamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrimidinamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4,6-dimethoxy-2-pyrimidinamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-furyl)-2-pyrimidinamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(2-thienyl)-2-pyrimidinamine,

30 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1H-purin-6-amine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methylthieno[2,3-d]pyrimidin-4-amine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-7-methylthieno[3,2-d]pyrimidin-4-amine,

5 N~7~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-9-methyl-9H-purin-6-amine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,

5-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,

10 6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-pyridinamine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzothiazol-2-amine,

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzoxazol-2-amine,

6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrazinamine,

15 6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-3-pyridazinamine,

6-((3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl)amino)-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione,

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,6-dimethoxy-4-pyrimidinamine,

N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine,

20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine,

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine,

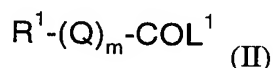
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine,

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-methyl-4-pyrimidinamine, and

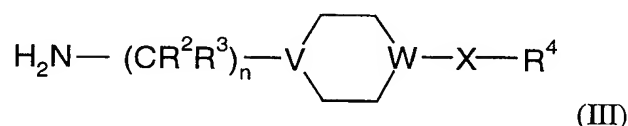
30 N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-N~2~-phenyl-2,4-pyrimidinediamine.

10. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises

(i) when T represents a group C(O)NH, reacting a compound of general formula

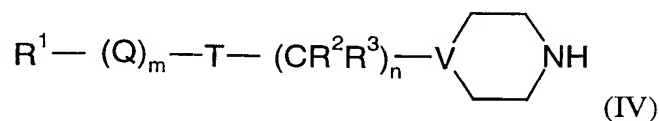


wherein  $L^1$  represents a leaving group (e.g. a hydroxyl or halide, such as chloride, group) and  $R^1$ , m and Q are as defined in formula (I), with a compound of general formula

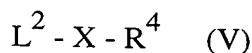


or an acid addition salt thereof (e.g. trifluoroacetate) wherein n,  $R^2$ ,  $R^3$ , V, W, X and  $R^4$  are as defined in formula (I); or

(ii) when T represents a group C(O)NH and W represents a nitrogen atom, reacting a compound of general formula

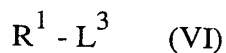


wherein  $R^1$ , m, Q, T, n,  $R^2$ ,  $R^3$  and V are as defined in formula (I), with a compound of general formula



wherein  $L^2$  represents a leaving group (e.g. a halogen atom) and X and  $R^4$  are as defined in formula (I); or

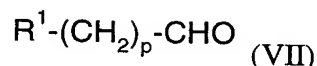
(iii) when T represents a group NH and m is 0, reacting a compound of general formula



wherein  $L^3$  represents a leaving group (e.g. a halogen atom) and  $R^1$  is as defined in formula (I), with a compound of formula (III) as defined in (i) above; or

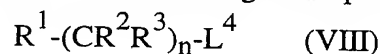


(iv) when T represents a group NH, m is 1 and Q represents C<sub>1</sub>-C<sub>4</sub> alkylene, reacting a compound of general formula

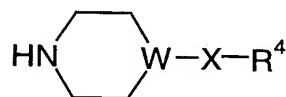


5 wherein p is 0, 1, 2 or 3 and R<sup>1</sup> is as defined in formula (I), with a compound of formula (III) as defined in (i) above; or

(v) when T represents a bond and m is 0, reacting a compound of general formula



10 wherein L<sup>4</sup> represents a leaving group such as a halogen atom (e.g. chlorine) and n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in formula (I), with a compound of general formula



15 (IX)

wherein W, X and R<sup>4</sup> are as defined in formula (I);

and optionally after (i), (ii), (iii), (iv) or (v) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or  
20 solvate of the compound of formula (I).

11. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

25

12. A process for the preparation of a pharmaceutical composition as claimed in claim 11 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 for use in therapy.
14. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in therapy.
15. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.
16. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00563

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, C07D 401/06, C07D 211/14, C07D 211/22, A61K 31/445,  
A61P 11/00, A61P 19/00, A61P 31/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5210086 A (PASCAL, GEORGE ET AL), 11 May 1993 (11.05.93) --	1-16
X	US 5143923 A (NICHOLAS J. HRIB ET AL), 1 Sept 1992 (01.09.92) --	1-16
X	US 4853393 A (ZIMMERMANN, MARKUS), 1 August 1989 (01.08.89) --	1-16
X	US 4335127 A (VANDERBERK JAN ET AL), 15 June 1982 (15.06.82) --	1-16

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

22 June 2000

Date of mailing of the international search report

04-08-2000

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00563

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9742956 A1 (SYNAPTIC PHARMACEUTICAL CORPORATION), 20 November 1997 (20.11.97) --	1-16
X	EP 0288563 A1 (EISAI CO., LTD), 2 November 1988 (02.11.88) --	1-16
X	EP 0184258 A2 (JANSSEN PHARMACEUTICA N.V.), 11 June 1986 (11.06.86) --	1-16
X	EP 0124476 A1 (CIBA-GEIGY AG), 7 November 1984 (07.11.84) --	1-16
X	FR 2724382 A1 (SYNTHELABO SOCIETE ANONYME), 15 March 1996 (15.03.96) --	1-16
X	STN International, File CAPLUS, CAPLUS accession no. 1997:259827, Document no. 127:17595, Kyorin Pharmaceutical Co., Ltd.: "Preparation of benzamide derivatives as gastrointestinal movement modulators" & JP,A2,09077742,19970325 --	1-16
X	STN International, File CAPLUS, CAPLUS accession no. 1997:204127, Document no. 126:212045, Yamonuchi Pharma Co Ltd: "Preparation of fused benzene ring derivatives as antidepressant drugs"; & JP,A2,09040646,19970210 --	1-16
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International application No.

PCT/SE 00/00563

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 37, 1994, Nicholas J. Hrib et al, "Benzisoxazole- and Benzisothiazole-3-carboxamides as Potential Atypical Antipsychotic Agents" page 2308 - page 2314 --	1-16
X	J. Med. Chem., Volume 35, 1992, Jeff L. Herndon et al, "Ketanserin Analogues: Structure-Affinity Relationships for 5-HT <sub>2</sub> and 5-HT <sub>1c</sub> serotonin receptor binding" page 4903 - page 4910 --	1-16
X	Journal of Labelled Compounds and Radiopharmaceuticals, Volume 25, No 7, November 1987, Cor G.M. Janssen et al, "Synthesis of 3H and 14C ketanserin" page 783 - page 792 -- -----	1-16

# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/SE00/00563**

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **16**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**See PCT Rule 39.1.(iv) .: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.**
2. ☒ Claims Nos.: **1-16**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**See extra sheet**
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE00/00563

Present claims 1-16 relate to an extremely large number of possible compounds. In fact, the claim contains so many options, variables, possible permutations and provisions that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, the search has been carried out for those parts of the application which appear to be clear and concise, namely the examples and closely related homologous compounds etc., those mentioned in the description.

"The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims(s) is impossible. Consequently, the search has been restricted.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

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